

Novel tricyclic spiropiperidines or spiropyrrolidines.

The present invention relates to novel compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

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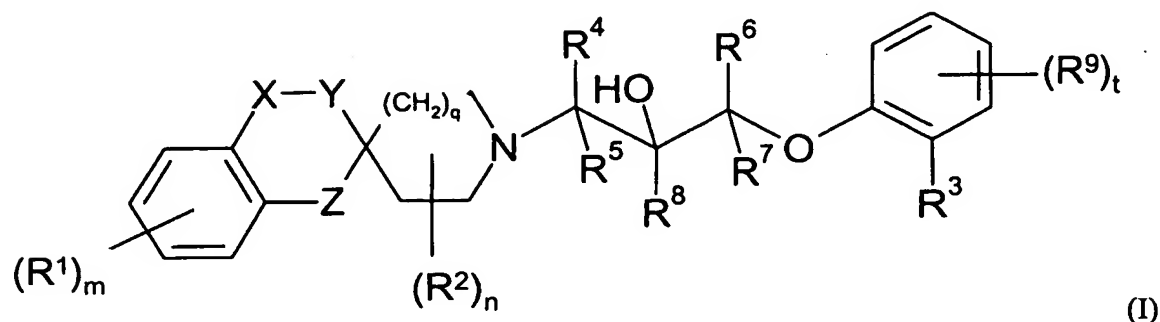
Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved
10 four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C) and Cys-Cys (C-C) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

15 The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and
20 MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1 α and 1 β (MIP-1 α and MIP-1 β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2,
25 CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

In accordance with the present invention, there is therefore provided a compound of formula



wherein

m is 0, 1, 2, 3 or 4;

each R^1 independently represents halogen, cyano, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy or sulphonamido ($-SO_2NH_2$);

either X represents a bond, $-CH_2-$, $-O-$ or $-C(O)-$ and Y represents a bond, $-CH_2-$, $-O-$ or $-C(O)-$, or X and Y together represent a group $-CH=C(CH_3)-$ or $-C(CH_3)=CH-$, and Z represents a bond, $-O-$, $-NH-$ or $-CH_2-$, provided that only one of X , Y and Z can represent a bond at any one time and provided that X and Y do not both simultaneously represent $-O-$ or $-C(O)-$;

n is 0, 1 or 2;

each R^2 independently represents halogen or C_1 - C_6 alkyl;

q is 0 or 1;

R^3 represents $-NHC(O)R^{10}$, $-C(O)NR^{11}R^{12}$ or $-COOR^{12a}$;

R^4 , R^5 , R^6 , R^7 and R^8 each independently represent a hydrogen atom or a C_1 - C_6 alkyl

group;

t is 0, 1 or 2;

each R^9 independently represents halogen, cyano, hydroxyl, carboxyl, C_1 - C_6 alkoxy, C_1 - C_6 alkoxycarbonyl, C_1 - C_6 haloalkyl, or C_1 - C_6 alkyl optionally substituted by at least one substituent selected from carboxyl and C_1 - C_6 alkoxycarbonyl;

R^{10} represents a group C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_6 cycloalkyl, adamantyl, C_5 - C_6 cycloalkenyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each of which may be optionally substituted by one or more substituents independently selected from nitro, hydroxyl, oxo, halogen, carboxyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_1 - C_6 alkylcarbonyl, C_1 - C_6 alkoxycarbonyl, phenyl and $-NHC(O)-R^{13}$, or

R^{10} represents a group $-NR^{14}R^{15}$ or $-OR^{16}$;

R^{11} and R^{12} each independently represent (i) a hydrogen atom, (ii) a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur and optionally further comprising a bridging group, the ring being optionally substituted with at least one substituent selected from halogen, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 hydroxyalkyl and C_1 - C_6 haloalkyl, (iii) a C_1 - C_6 alkyl group optionally substituted by at least one substituent selected from halogen, amino ($-NH_2$), hydroxyl, C_1 - C_6 haloalkyl, carboxyl, C_1 - C_6 alkoxy, C_1 - C_6 alkoxycarbonyl, C_1 - C_6 alkylcarbonylamino and a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur and optionally further comprising a bridging group, the ring being optionally substituted with at least one substituent selected from halogen, hydroxyl, oxo ($=O$), C_1 - C_6 alkyl, C_1 - C_6 hydroxyalkyl and C_1 - C_6 haloalkyl, or

(iv) C_1 - C_6 alkylsulphonyl, or

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom and that is optionally fused to a benzene ring to form a 8- to 11-membered ring system, the heterocyclic ring or ring system being optionally substituted with at least one substituent selected from halogen, hydroxyl, amido ($-CONH_2$), C_1 - C_6 alkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkoxycarbonyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkylamino, di- C_1 - C_6 alkylamino, C_1 - C_6 alkylcarbonyl, C_1 - C_6 alkylcarbonylamino, C_1 - C_6 alkylaminocarbonyl, di- C_1 - C_6 alkylaminocarbonyl, phenyl, halophenyl, phenylcarbonyl, phenylcarbonyloxy and hydroxydiphenylmethyl;

R^{12a} represents a hydrogen atom or a C_1 - C_6 alkyl group;

R^{13} represents a C_1 - C_6 alkyl, amino ($-NH_2$) or phenyl group;

R^{14} and R^{15} each independently represent a hydrogen atom, or a group C_1 - C_6 alkyl, C_1 - C_6 alkylsulphonyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted as defined above for R^{10} , or R^{14} and R^{15} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom, the heterocyclic ring being optionally substituted by at least one hydroxyl; and

R^{16} represents a hydrogen atom, or a group C_1 - C_6 alkyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted as defined above for R^{10} ;

or a pharmaceutically acceptable salt or solvate thereof.

In the context of the present specification, unless otherwise stated, an alkyl or alkenyl substituent group or an alkyl moiety in a substituent group may be linear or branched. The alkyl moieties in a di-alkylamino or di-alkylaminocarbonyl substituent group may be the same or different. A haloalkyl or halophenyl substituent group will comprise at least one halogen atom, e.g. one, two, three or four halogen atoms. A hydroxyalkyl substituent may contain one or more hydroxyl groups but preferably contains one or two hydroxyl groups. In the ring substituted by R^2 , R^2 may be attached to any suitable ring carbon atom including the carbon atom of $(CH_2)_q$. When R^{11} and R^{12} or R^{14} and R^{15} represent a 4- to

7-membered saturated heterocycle, it should be understood that the heterocycle will contain no more than two ring heteroatoms: the nitrogen ring atom to which R^{11} and R^{12} or R^{14} and R^{15} are attached and optionally a nitrogen, oxygen or sulphur ring atom. In the definition of R^{10} (or R^{14} , R^{15} or R^{16}) it should be noted that the saturated or unsaturated 5- to 10-membered heterocyclic ring system may have alicyclic or aromatic properties.

Similarly, in the definition of R^{11} or R^{12} , a 3- to 6-membered saturated or unsaturated ring

optionally comprising at least one ring heteroatom may have alicyclic or aromatic properties. An unsaturated ring system will be partially or fully unsaturated.

In an embodiment of the invention, m is 0 or 1.

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Each R^1 independently represents halogen (e.g. chlorine, fluorine, bromine or iodine), cyano, hydroxyl, C_1-C_6 , preferably C_1-C_4 , alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6 , preferably C_1-C_4 , haloalkyl (e.g. trifluoromethyl), C_1-C_6 , preferably C_1-C_4 , alkoxy (e.g. methoxy, ethoxy, n-propoxy or
10 n-butoxy) or sulphonamido.

In an embodiment of the invention, each R^1 independently represents halogen, C_1-C_6 , preferably C_1-C_4 , alkyl or C_1-C_6 , preferably C_1-C_4 , haloalkyl.

15 In another embodiment, each R^1 independently represents fluorine, chlorine, methyl or trifluoromethyl.

Combinations of X and Y of particular interest include any one or more of the following:

X	Y
bond	O
O	bond
CH ₂	bond
bond	CH ₂
CH ₂	O
O	CH ₂
C(O)	O
O	C(O)
CH ₂	CH ₂
-CH=C(CH ₃)-	

In an embodiment of the invention, X and Y have the meanings shown below:

X	Y
bond	O
O	bond
CH ₂	O
O	CH ₂
C(O)	O
O	C(O)
CH ₂	CH ₂
-CH=C(CH ₃)-	

- 5 In an embodiment of the invention, Z represents a bond, -O- or -CH₂-.

Combinations of X, Y and Z of particular interest include any one or more of the following:

X	Y	Z
bond	O	CH ₂
O	bond	CH ₂
CH ₂	bond	O
bond	CH ₂	O
CH ₂	O	bond
C(O)	O	bond
O	C(O)	bond
CH ₂	CH ₂	bond
O	bond	O
bond	O	O
CH ₂	CH ₂	O
O	CH ₂	CH ₂
-CH=C(CH ₃)-		bond

In an embodiment of the invention, X, Y and Z have the meanings shown below:

X	Y	Z
bond	O	CH ₂
O	bond	CH ₂
CH ₂	O	bond
O	CH ₂	bond
C(O)	O	bond
O	C(O)	bond
CH ₂	CH ₂	bond
bond	O	O
O	bond	O
-CH=C(CH ₃)-		bond

In another embodiment of the invention, X, Y and Z have the meanings shown below:

X	Y	Z
bond	O	CH ₂
O	bond	CH ₂
CH ₂	bond	O
bond	CH ₂	O
CH ₂	O	bond

In still another embodiment of the invention, X, Y and Z have the following meanings:

X	Y	Z
bond	O	CH ₂
O	bond	CH ₂
CH ₂	O	bond

Each R² independently represents halogen (e.g. chlorine, fluorine, bromine or iodine) or C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

In an embodiment of the invention, n is 1 and R² represents halogen, particularly fluorine.

In an embodiment of the invention, R³ represents -NHC(O)R¹⁰.

In another embodiment of the invention, R³ represents -C(O)NR¹¹R¹².

R⁴, R⁵, R⁶, R⁷ and R⁸ each independently represent a hydrogen atom or a C₁-C₆, preferably C₁-C₄, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

In an embodiment of the invention, R^4 , R^5 , R^6 , R^7 and R^8 each independently represent a hydrogen atom or a methyl group.

- 5 In another embodiment of the invention, R^4 , R^5 , R^6 and R^7 each represent a hydrogen atom and R^8 represents a methyl group.

In an embodiment of the invention, R^4 , R^5 , R^6 , R^7 and R^8 each represent a hydrogen atom.

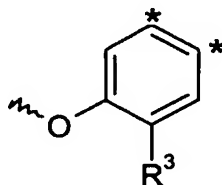
- 10 In an embodiment of the invention, t is 0, 1 or 2.

- Each R^9 independently represents halogen (e.g. chlorine, fluorine, bromine or iodine), cyano, hydroxyl, carboxyl, C_1 - C_6 , preferably C_1 - C_4 , alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1 - C_6 , preferably C_1 - C_4 , alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl or n-butoxycarbonyl), C_1 - C_6 , preferably C_1 - C_4 , haloalkyl (e.g. trifluoromethyl), or C_1 - C_6 , preferably C_1 - C_4 , alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by at least one substituent (e.g. one, two or three substituents) independently selected from carboxyl and C_1 - C_6 , preferably C_1 - C_4 , alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl or n-butoxycarbonyl).
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In an embodiment of the invention, each R^9 independently represents halogen, cyano, hydroxyl, carboxyl, C_1 - C_6 , preferably C_1 - C_4 , alkoxy, C_1 - C_6 , preferably C_1 - C_4 , alkoxycarbonyl, C_1 - C_6 , preferably C_1 - C_4 , haloalkyl or C_1 - C_6 , preferably C_1 - C_4 , alkyl.

- 25 In another embodiment of the invention, each R^9 independently represents halogen, hydroxyl, carboxyl, methyl, methoxy, methoxycarbonyl or trifluoromethyl.

R^9 is preferably bound to a carbon atom located in the *para* position with respect to the carbon atom to which either the oxygen atom or the group R^3 is bound, as indicated by the asterisks in the partial structure shown below:



R^{10} may represent a group C_1 - C_6 , preferably C_1 - C_4 , alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_2 - C_6 , preferably C_2 - C_4 , alkenyl, C_3 - C_6 cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), adamantyl, C_5 - C_6 cycloalkenyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, each of which (i.e. each of the recited groups and the ring system) may be optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from nitro, hydroxyl, oxo, halogen (e.g. fluorine, chlorine, bromine or iodine), carboxyl, C_1 - C_6 , preferably C_1 - C_4 , alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1 - C_6 , preferably C_1 - C_4 , alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1 - C_6 , preferably C_1 - C_4 , alkylthio (e.g. methylthio or ethylthio), C_1 - C_6 , preferably C_1 - C_4 , alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, n-pentylcarbonyl or n-hexylcarbonyl), C_1 - C_6 , preferably C_1 - C_4 , alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), phenyl and $-NHC(O)-R^{13}$.

The saturated or unsaturated 5- to 10-membered heterocyclic ring system in R^{10} may be monocyclic or polycyclic (e.g. bicyclic), examples of which include pyrrolidinyl, piperidinyl, pyrazolyl, thiazolidinyl, thienyl, isoxazolyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, quinolinyl, benzimidazolyl, triazolyl, tetrazolyl, pyridinyl and combinations of any two or more thereof.

In an embodiment of the invention, R^{10} represents a group C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, phenyl or a saturated or unsaturated 5- to 6-membered heterocyclic ring system comprising at least one ring heteroatom (e.g. one or two ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, each of which (i.e. each of the recited groups and the ring system) may be optionally substituted by one, two, three or four substituents independently selected from nitro, hydroxyl, oxo, halogen, carboxyl, C_1 - C_6 , preferably C_1 - C_4 , alkyl, C_1 - C_6 , preferably C_1 - C_4 , alkoxy, C_1 - C_6 , preferably C_1 - C_4 , alkylthio, C_1 - C_6 , preferably C_1 - C_4 , alkylcarbonyl, C_1 - C_6 , preferably C_1 - C_4 , alkoxycarbonyl, phenyl and $-NHC(O)-R^{13}$.

In another embodiment of the invention, R^{10} represents a group C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl or phenyl, each of which may be optionally substituted by one or two substituents independently selected from halogen, C_1 - C_6 , preferably C_1 - C_4 , alkyl and C_1 - C_6 , preferably C_1 - C_4 , alkoxy.

In still another embodiment of the invention, R^{10} represents C_1 - C_6 alkyl, cyclopentyl or phenyl.

Alternatively, R^{10} may represent a group $-NR^{14}R^{15}$ or $-O-R^{16}$.

R^{14} and R^{15} each independently represent a hydrogen atom, or a group C_1 - C_6 , preferably C_1 - C_4 , alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1 - C_6 , preferably C_1 - C_4 , alkylsulphonyl (e.g. methylsulphonyl, ethylsulphonyl, n-propylsulphonyl, isopropylsulphonyl, n-butylsulphonyl, isobutylsulphonyl, tert-butylsulphonyl, n-pentylsulphonyl or n-hexylsulphonyl), phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, each group (i.e. each of the recited groups including the ring system) being optionally substituted as defined above for R^{10} (that is, optionally substituted with one or more (e.g. one, two, three or four) substituents independently

selected from nitro, hydroxyl, oxo, halogen (e.g. fluorine, chlorine, bromine or iodine), carboxyl, C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C₁-C₆, preferably C₁-C₄, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C₁-C₆, preferably C₁-C₄, alkylthio (e.g. methylthio or ethylthio), C₁-C₆, preferably C₁-C₄, alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, n-pentylcarbonyl or n-hexylcarbonyl), C₁-C₆, preferably C₁-C₄, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), phenyl and -NHC(O)-R¹³, or R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom (e.g. pyrrolidinyl, piperidinyl, morpholino, piperazinyl or thiomorpholinyl), the heterocyclic ring being optionally substituted by at least one hydroxyl (e.g. one or two hydroxyls).

In R¹⁴ or R¹⁵, the saturated or unsaturated 5- to 10-membered heterocyclic ring system may be monocyclic or polycyclic (e.g. bicyclic), examples of which include pyrrolidinyl, piperidinyl, pyrazolyl, thiazolidinyl, thienyl, isoxazolyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, quinolinyl, benzimidazolyl, triazolyl, tetrazolyl, pyridinyl and combinations of any two or more thereof.

In an embodiment of the invention, R¹⁴ and R¹⁵ each independently represent a hydrogen atom or a C₁-C₆ alkyl or C₁-C₆ alkylsulphonyl group, each group being optionally substituted as defined above for R¹⁰, or R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a 5- to 6-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom, the heterocyclic ring being optionally substituted by at least one hydroxyl.

In a further embodiment, R¹⁴ and R¹⁵ each independently represent a hydrogen atom or a C₁-C₆ alkylsulphonyl group, or R¹⁴ and R¹⁵ together with the nitrogen atom to which

they are attached form a 5- to 6-membered saturated heterocyclic ring that is optionally substituted by at least one hydroxyl.

In a still further embodiment, R¹⁴ and R¹⁵ each independently represent a hydrogen atom or a methylsulphonyl group, or R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a pyrrolidinyl or piperidinyl ring optionally substituted by one hydroxyl group.

R¹⁶ represents a hydrogen atom, or a group C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, each group (i.e. each of the recited groups including the ring system) being optionally substituted as defined above for R¹⁰ (that is, optionally substituted with one or more (e.g. one, two, three or four) substituents independently selected from nitro, hydroxyl, oxo, halogen (e.g. fluorine, chlorine, bromine or iodine), carboxyl, C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C₁-C₆, preferably C₁-C₄, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C₁-C₆, preferably C₁-C₄, alkylthio (e.g. methylthio or ethylthio), C₁-C₆, preferably C₁-C₄, alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, n-pentylcarbonyl or n-hexylcarbonyl), C₁-C₆, preferably C₁-C₄, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), phenyl and -NHC(O)-R¹³).

In R¹⁶, the saturated or unsaturated 5- to 10-membered heterocyclic ring system may be monocyclic or polycyclic (e.g. bicyclic), examples of which include pyrrolidinyl, piperidinyl, pyrazolyl, thiazolidinyl, thienyl, isoxazolyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, quinolinyl, benzimidazolyl, triazolyl, tetrazolyl, pyridinyl and combinations of any two or more thereof.

R¹¹ and R¹² each independently represent

(i) a hydrogen atom,

(ii) a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur and optionally further comprising a bridging group (examples of which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, phenyl, pyrrolyl, imidazolyl, pyridinyl, pyrazinyl, pyridazinyl, tetrazolyl, pyrimidinyl, thienyl, furanyl, tetrahydrofuranyl and combinations of any two or more thereof), the ring being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl, C₁-C₆, preferably C₁-C₅, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 1,1-dimethylpropyl or n-hexyl), C₁-C₆, preferably C₁-C₄, hydroxyalkyl (e.g. -CH₂OH, -CH₂CH₂OH, -CH₂CH₂CH₂OH or -CH(OH)CH₃) and C₁-C₆, preferably C₁-C₄, haloalkyl (e.g. trifluoromethyl),

(iii) a C₁-C₆ alkyl group optionally substituted by at least one substituent (e.g. one, two, three or four substituents independently) selected from halogen (e.g. fluorine, chlorine, bromine or iodine), amino (-NH₂), hydroxyl, C₁-C₆, preferably C₁-C₄, haloalkyl (e.g. trifluoromethyl), carboxyl, C₁-C₆, preferably C₁-C₄, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C₁-C₆, preferably C₁-C₄, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), C₁-C₆, preferably C₁-C₄, alkylcarbonylamino (e.g.

methylcarbonylamino or ethylcarbonylamino) and a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur and optionally further comprising a bridging group (examples of which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, phenyl, pyrrolyl, imidazolyl, pyridinyl, pyrazinyl, pyridazinyl, tetrazolyl, pyrimidinyl, thienyl, furanyl, tetrahydrofuranyl and combinations of any two or more thereof), the ring being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl, oxo (=O),

C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl,

tert-butyl, n-pentyl or n-hexyl), C₁-C₆, preferably C₁-C₄, hydroxyalkyl (e.g. -CH₂OH, -CH₂CH₂OH, -CH₂CH₂CH₂OH or -CH(OH)CH₃) and C₁-C₆, preferably C₁-C₄, haloalkyl (e.g. trifluoromethyl), or

- (iv) C₁-C₆, preferably C₁-C₄, alkylsulphonyl (e.g. methylsulphonyl or ethylsulphonyl), or
 5 R¹¹ and R¹² together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom (e.g. pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or thiomorpholinyl) and that is optionally fused to a benzene ring to form a 8- to 11-membered ring system (e.g. dihydroisoquinolinyl or dihydroisoindolyl), the heterocyclic
 10 ring or ring system being optionally substituted with at least one substituent (e.g. one, two, three or four substituents independently) selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl, amido (-CONH₂), C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C₁-C₆, preferably C₁-C₄, hydroxyalkyl (e.g. -CH₂OH, -CH₂CH₂OH, -CH₂CH₂CH₂OH
 15 or -CH(OH)CH₃), C₁-C₆, preferably C₁-C₄, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C₁-C₆, preferably C₁-C₄, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), C₁-C₆, preferably C₁-C₄, haloalkyl (e.g. trifluoromethyl), C₁-C₆, preferably C₁-C₄, alkylamino (e.g. methylamino or ethylamino), di-C₁-C₆, preferably C₁-C₄, alkylamino (e.g. dimethylamino), C₁-C₆, preferably C₁-C₄, alkylcarbonyl (e.g. methylcarbonyl or ethylcarbonyl),
 20 methylcarbonyl or ethylcarbonyl), C₁-C₆, preferably C₁-C₄, alkylcarbonylamino (e.g. methylcarbonylamino or ethylcarbonylamino), C₁-C₆, preferably C₁-C₄, alkylaminocarbonyl (e.g. methylaminocarbonyl or ethylaminocarbonyl), di-C₁-C₆, preferably C₁-C₄, alkylaminocarbonyl (e.g. dimethylaminocarbonyl), phenyl, halophenyl (e.g. fluorophenyl or chlorophenyl), phenylcarbonyl, phenylcarbonyloxy and
 25 hydroxydiphenylmethyl.

In an embodiment of the invention, R¹¹ and/or R¹² represents a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and
 30 sulphur and optionally further comprising a bridging group, the ring being optionally

substituted with at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, C₁-C₆, preferably C₁-C₅, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 1,1-dimethylpropyl or n-hexyl) and C₁-C₆, preferably C₁-C₄, hydroxyalkyl (e.g. -CH₂OH, -CH₂CH₂OH, -CH₂CH₂CH₂OH or -CH(OH)CH₃).

In a further embodiment of the invention, R¹¹ and/or R¹² represents a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring nitrogen atom and optionally further comprising a bridging group (in particular, cyclopropyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, phenyl, pyrrolidinyl and tetrazolyl), the ring being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, C₁-C₅ alkyl and C₁-C₂ hydroxyalkyl.

In an embodiment of the invention, R¹¹ and/or R¹² represents a C₁-C₆ alkyl group optionally substituted by at least one substituent (e.g. one, two, three or four substituents independently) selected from amino, hydroxyl, C₁-C₆, preferably C₁-C₄, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C₁-C₆, preferably C₁-C₄, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), C₁-C₆, preferably C₁-C₄, alkylcarbonylamino (e.g. methylcarbonylamino or ethylcarbonylamino) and a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen and oxygen and optionally further comprising a bridging group, the ring being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl, oxo, C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C₁-C₆, preferably C₁-C₄, hydroxyalkyl (e.g. -CH₂OH, -CH₂CH₂OH, -CH₂CH₂CH₂OH or -CH(OH)CH₃) and C₁-C₆, preferably C₁-C₄, haloalkyl (e.g. trifluoromethyl).

In another embodiment of the invention, R¹¹ and/or R¹² represents a C₁-C₆ alkyl group optionally substituted by at least one substituent (e.g. one, two, three or four substituents

independently) selected from amino, hydroxyl, C₁-C₄ alkoxy, C₁-C₂ alkoxycarbonyl, C₁-C₂ alkylcarbonylamino and a 3- to 6-membered saturated or unsaturated ring optionally comprising one or two ring heteroatoms selected from nitrogen and oxygen and optionally further comprising a bridging group (in particular, cyclopropyl, bicyclo[2.2.1]heptyl, phenyl or tetrahydrofuranyl), the ring being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from oxo (e.g. to form a 2,5-dioxoimidazolidinyl ring) and C₁-C₂ alkyl.

In an embodiment of the invention, R¹¹ and R¹² together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom (e.g. pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or thiomorpholinyl) and that is optionally fused to a benzene ring to form a 8- to 11-membered ring system (e.g. dihydroisoquinolinyl or dihydroisoindolyl), the heterocyclic ring or ring system being optionally substituted with at least one substituent (e.g. one, two, three or four substituents independently) selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl, amido, C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C₁-C₆, preferably C₁-C₄, hydroxyalkyl (e.g. -CH₂OH, -CH₂CH₂OH, -CH₂CH₂CH₂OH or -CH(OH)CH₃), C₁-C₆, preferably C₁-C₄, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C₁-C₆, preferably C₁-C₄, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), C₁-C₆, preferably C₁-C₄, haloalkyl (e.g. trifluoromethyl), di-C₁-C₆, preferably C₁-C₄, alkylamino (e.g. dimethylamino), C₁-C₆, preferably C₁-C₄, alkylcarbonylamino (e.g. methylcarbonylamino or ethylcarbonylamino), di-C₁-C₆, preferably C₁-C₄, alkylaminocarbonyl (e.g. dimethylaminocarbonyl), phenyl, halophenyl (e.g. fluorophenyl or chlorophenyl), phenylcarbonyloxy and hydroxydiphenylmethyl.

In an embodiment of the invention, R¹¹ and R¹² together with the nitrogen atom to which they are attached form a 5- to 6-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom and that is optionally fused to a

benzene ring to form a 9- to 10-membered ring system, the heterocyclic ring or ring system being optionally substituted with one or two substituents independently selected from fluorine, hydroxyl, amido, C₁-C₂ alkyl, C₁-C₂ hydroxyalkyl, C₁-C₂ alkoxy, C₁-C₂ alkoxycarbonyl, C₁-C₂ haloalkyl, di-C₁-C₂ alkylamino, C₁-C₂ alkylcarbonylamino, di-C₁-C₂ alkylaminocarbonyl, phenyl, chlorophenyl, phenylcarbonyloxy and hydroxydiphenylmethyl.

In another embodiment of the invention, R¹¹ and R¹² together with the nitrogen atom to which they are attached form a heterocyclic ring or ring system selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dihydroisoquinolinyl and dihydroisoindolyl, the heterocyclic ring or ring system being optionally substituted with one or two substituents independently selected from fluorine, hydroxyl, amido, methyl, hydroxymethyl, 2-hydroxyethyl, methoxy, methoxycarbonyl, trifluoromethyl, dimethylamino, methylcarbonylamino, dimethylaminocarbonyl, phenyl, chlorophenyl, phenylcarbonyloxy and hydroxydiphenylmethyl.

R^{12a} represents a hydrogen atom or a C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) group.

In an embodiment of the invention, R^{12a} represents a hydrogen atom or methyl group.

R¹³ represents a C₁-C₆, preferably C₁-C₄, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), amino or phenyl group.

In an embodiment of the invention:

each R¹ independently represents halogen or C₁-C₆ alkyl;

either one of X and Y represents a bond and the other of X and Y represents an oxygen atom and Z represents -CH₂-, or X represents -CH₂-, Y represents an oxygen atom and Z represents a bond;

R^4 , R^5 , R^6 and R^7 each represent a hydrogen atom and R^8 represents a hydrogen atom or a C_1 - C_6 alkyl group;

t is 1 or 2; and

each R^9 independently represents hydroxyl (e.g. in the *para* position with respect to R^3) or
 5 halogen (e.g. either in the *para* position with respect to R^3 or in the *para* position with respect to -O-).

In an embodiment of the invention:

m is 0 or 1;

10 each R^1 independently represents fluorine, chlorine, methyl or trifluoromethyl;

either X represents a bond, -CH₂-, -O- or -C(O)- and Y represents a bond, -CH₂-, -O- or -C(O)-, or X and Y together represent a group -CH=C(CH₃)-, and Z represents a bond, -O-, or -CH₂-, provided that only one of X, Y and Z can represent a bond at any one time and provided that X and Y do not both simultaneously represent -O- or -C(O)-;

15 n is 0 or 1;

R^2 represents fluorine;

q is 0 or 1;

R^3 represents -NHC(O) R^{10} , -C(O)NR¹¹ R^{12} or -COOR^{12a};

R^4 , R^5 , R^6 , R^7 and R^8 each independently represent a hydrogen atom or a methyl
 20 group;

t is 0, 1 or 2;

each R^9 independently represents halogen, hydroxyl, carboxyl, methyl, methoxy, methoxycarbonyl or trifluoromethyl;

R^{10} represents a methyl, cyclopentyl, phenyl or a group -NR¹⁴ R^{15} ;

25 R^{11} and R^{12} each independently represent (i) a hydrogen atom,

(ii) a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring nitrogen atom and optionally further comprising a bridging group, the ring being optionally substituted with at least one substituent selected from hydroxyl, C_1 - C_5 alkyl and C_1 - C_2 hydroxyalkyl,

30 (iii) C_1 - C_6 alkyl group optionally substituted by at least one substituent selected from

amino, hydroxyl, C₁-C₄ alkoxy, C₁-C₂ alkoxy carbonyl, C₁-C₂ alkyl carbonylamino and a 3- to 6-membered saturated or unsaturated ring optionally comprising one or two ring heteroatoms selected from nitrogen and oxygen and optionally further comprising a bridging group, the ring being optionally substituted with at least one substituent selected from oxo and C₁-C₂ alkyl, or (iv) methylsulphonyl, or R¹¹ and R¹² together with the nitrogen atom to which they are attached form a 5- to 6-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom and that is optionally fused to a benzene ring to form a 9- to 10-membered ring system, the heterocyclic ring or ring system being optionally substituted with one or two substituents independently selected from fluorine, hydroxyl, amido, C₁-C₂ alkyl, C₁-C₂ hydroxyalkyl, C₁-C₂ alkoxy, C₁-C₂ alkoxy carbonyl, C₁-C₂ haloalkyl, di-C₁-C₂ alkylamino, C₁-C₂ alkyl carbonylamino, di-C₁-C₂ alkylaminocarbonyl, phenyl, chlorophenyl, phenylcarbonyloxy and hydroxydiphenylmethyl;

R^{12a} represents a hydrogen atom or a methyl group; and R¹⁴ and R¹⁵ each independently represent a hydrogen atom or a C₁-C₆ alkylsulphonyl group, or R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a 5- to 6-membered saturated heterocyclic ring that is optionally substituted by at least one hydroxyl.

In an embodiment of the invention:

m is 0 or 1;

R¹ represents halogen;

either X represents a bond, -CH₂-, -O- or -C(O)- and Y represents a bond, -CH₂-, -O- or -C(O)-, or X and Y together represent a group -CH=C(CH₃)-, and Z represents a bond, -O- or -CH₂-, provided that only one of X, Y and Z can represent a bond at any one time and provided that X and Y do not both simultaneously represent -O- or -C(O)-;

n is 0;

q is 0 or 1;

R³ represents -NHC(O)R¹⁰, -C(O)NR¹¹R¹² or -COOR^{12a};

R^4 , R^5 , R^6 , R^7 and R^8 each independently represent a hydrogen atom or a methyl group;

t is 0 or 1;

R^9 represents halogen, hydroxyl, methoxy or trifluoromethyl;

5 R^{10} represents methyl;

R^{11} and R^{12} each independently represent hydrogen, methyl, cyclopropyl, hydroxyethyl or aminoethyl, or R^{11} and R^{12} together with the nitrogen atom to which they are attached form a morpholinyl group, or form a piperidinyl group substituted by hydroxyl; and

10 R^{12a} represents a hydrogen atom.

Examples of compounds of the invention include:

N-(2-([(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide,

15 *N*-(2-([(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorophenyl)acetamide,

N-(2-([(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-methoxyphenyl)acetamide,

20 *N*-(2-([(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)acetamide,

N-(2-([(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-5-(trifluoromethyl)phenyl)acetamide,

2-([(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-cyclopropylbenzamide,

25 2-([(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-cyclopropyl-4-fluorobenzamide,

2-([(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-cyclopropyl-4-methoxybenzamide,

30 *N*-(2-([(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-4-hydroxyphenyl)acetamide trifluoroacetate,

N-(5-Chloro-2-{[(2*S*)-3-(6-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide,

N-(2-{[(2*S*)-3-(6-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorophenyl)acetamide,

5 *N*-(2-{[(2*S*)-3-(6-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide,

N-(2-{[(2*S*)-3-(6-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-methoxyphenyl)acetamide,

10 2-{[(2*S*)-3-(6-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-cyclopropyl-4-fluorobenzamide,

N-(2{[(2*S*)-3-(5-Fluoro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]phenyl)acetamide,

N-(4-Chloro-2-{[(2*S*)-2-hydroxy-3-(3-oxo-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide,

15 *N*-Cyclopropyl-2-{[(2*S*)-2-hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}benzamide,

N-(4-Chloro-2-{[(2*S*)-2-hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide,

20 *N*-(5-Chloro-2{[(2*S*)-2-hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide,

N-(2-{[(2*S*)-2-hydroxy-2-methyl-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide,

N-[2-{[(2*S*)-2-Hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}-5-(trifluoromethyl)phenyl]acetamide,

25 *N*-(2-{[(2*S*)-2-Hydroxy-3-(2-methyl-1'*H*-spiro[indene-1,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide,

N-(2-{[(2*S*)-3-(2,3-Dihydro-1'*H*-spiro[indene-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide,

30 *N*-(2-{[(2*S*)-2-Hydroxy-3-(2-oxo-1'*H*-spiro[1-benzofuran-3,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide,

2-{{{(2S)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-N-cyclopropyl-4-hydroxybenzamide,

2-{{{(2S)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl}oxy}-N-cyclopropyl-4-hydroxybenzamide,

5 N-(4-hydroxy-2-{{{(2S)-2-hydroxy-3-(1'H,4H-spiro[chromene-3,4'-piperidin]-1'-yl)propyl}oxy}phenyl)acetamide,

2-{{{(2S)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl}oxy}-4-hydroxy-N-methylbenzamide (trifluoroacetate),

10 2-{{{(2S)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy}oxy}-4-hydroxy-N-methylbenzamide,

N-(2-{{{(2S)-3-(5-Chloro-1'H-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxyphenyl)acetamide trifluoroacetate,

N-(2-{{{(2S)-3-(5-Chloro-1'H-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl}oxy}-4-hydroxyphenyl)acetamide trifluoroacetate,

15 N-(4-Hydroxy-2-{{{(2S)-2-hydroxy-3-(1'H-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)propyl}oxy}phenyl)acetamide trifluoroacetate,

N-(4-Hydroxy-2-{{{(2S)-2-hydroxy-2-methyl-3-(1'H-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)propyl}oxy}phenyl)acetamide trifluoroacetate,

20 N-(2-{{{(2S)-3-(5-Chloro-1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxyphenyl)acetamide,

N-(2-{{{(2S)-3-(5-Chloro-1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}phenyl)acetamide,

2-{{{(2S)-3-(5-Chloro-1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-methylbenzamide,

25 2-{{{(2S)-3-(5-Chloro-1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxy-2-methoxypropyl}oxy}-N-cyclopropyl-4-hydroxybenzamide,

2-{{{(2S)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-(2-hydroxyethyl)benzamide,

30 N-(2-Aminoethyl)-2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzamide,

2-{{{[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-methylbenzamide,

N-(2-{{{[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)acetamide,

5 *N*-(2-{{{[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide,

N-[2-({[(2S)-3-[(2S)-5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)phenyl]acetamide,

10 *N*-[2-({[(2S)-3-[(2R)-5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)phenyl]acetamide,

N-[2-({[(2S)-3-[(2S)-5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)-4-methoxyphenyl]acetamide,

N-[2-({[(2S)-3-[(2R)-5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)-4-methoxyphenyl]acetamide,

15 2-{{{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-methylbenzamide,

2-{{{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoic acid (trifluoroacetate),

20 3(S)-1-(2-{{{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)pyrrolidin-3-ol,

3(R)-1-(2-{{{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)pyrrolidin-3-ol,

3-{{{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-(morpholin-4-ylcarbonyl)phenol,

25 2-{{{[(2S)-3-(5-chloro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-methylbenzamide trifluoroacetate,

N-(2-{{{[(2S)-3-(6-chloro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide trifluoroacetate,

30 *N*-(2-{{{[(2S)-3-(6-chloro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorophenyl)acetamide trifluoroacetate,

2-{{{(2S)-3-(6-chloro-3,4-dihydro-1'H-spiro[chromene-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-N-methylbenzamide trifluoroacetate,

N-(2-{{{(2S)-3-(6-chloro-3,4-dihydro-1'H-spiro[chromene-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxyphenyl)acetamide trifluoroacetate,

5 *N*-(2-{{{(2S)-3-(6-chloro-3,4-dihydro-1'H-spiro[chromene-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl}oxy}-4-hydroxyphenyl)acetamide trifluoroacetate,

N-[2-{{{(2S)-3-[(2R)-5-chloro-1'H,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)-4-hydroxyphenyl]acetamide,

10 *N*-[2-{{{(2S)-3-[(2S)-5-chloro-1'H,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)-4-hydroxyphenyl]acetamide,

3-{{{(2S)-3-(5-Chloro-1'H,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-(pyrrolidin-1-ylcarbonyl)phenol,

1-(2-{{{(2S)-3-(5-Chloro-1'H,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)piperidin-4-ol,

15 (3S)-1-(2-{{{(2S)-3-(5-Chloro-1'H,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}benzoyl)pyrrolidin-3-ol,

3-{{{(2S)-3-(5-Chloro-1'H,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-(piperidin-1-ylcarbonyl)phenol,

20 (3S)-1-(2-{{{(2S)-3-(5-Chloro-1'H,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)pyrrolidin-3-ol,

1-(2-{{{(2S)-3-(5-Chloro-1'H,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)piperidin-4-ol,

N-[4-Hydroxy-2-{{{(2S)-2-hydroxy-3-[5-(trifluoromethyl)-1'H,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl]propyl}oxy)phenyl]acetamide,

25 (3S)-1-(2-{{{(2S)-3-(5-Chloro-1'H,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)pyrrolidin-3-ylbenzoate,

(3S)-1-(2-{{{(2S)-3-(5-Chloro-1'H,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-fluorobenzoyl)pyrrolidin-3-ol,

30 (3S)-1-[4-Hydroxy-2-{{{(2S)-2-hydroxy-3-[5-(trifluoromethyl)-1'H,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl]propyl}oxy}benzoyl]pyrrolidin-3-ol,

(3S)-1-(4-Fluoro-2-{{(2S)-2-hydroxy-3-(1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}benzoyl)pyrrolidin-3-ol,

4-Fluoro-2-{{(2S)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}benzoic acid (hydrochloride),

5 (3S)-1-(4-Fluoro-2-{{(2S)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}benzoyl)pyrrolidin-3-ol,

N-[(3S)-1-(2-{{(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)pyrrolidin-3-yl]acetamide,

10 2-{{(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-methylbenzoic acid hydrochloride,

(3S)-1-(2-{{(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy})-4-methylbenzoyl)pyrrolidin-3-ol,

2-{{(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-methylbenzoic acid hydrochloride,

15 (2S)-1-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-(2-{{2-(hydroxymethyl)morpholin-4-yl}carbonyl}-5-methylphenoxy)propan-2-ol,

(3S)-1-(2-{{(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-methylbenzoyl)pyrrolidin-3-ol,

20 2-{{(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-*N*-{[(4*R*)-2,5-dioxoimidazolidin-4-yl]methyl}-4-hydroxybenzamide,

1-(2-{{(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)-3-(trifluoromethyl)pyrrolidin-3-ol,

3-{{(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-{{3-(trifluoromethyl)pyrrolidin-1-yl}carbonyl} phenol,

25 *N*-[2-(Acetylamino)ethyl]-2-{{(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzamide,

N-(5-chloro-2-{{(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-methoxyphenyl)acetamide,

30 (3S)-*N*-(5-chloro-2-{{(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}phenyl)-3-hydroxypyrrrolidine-1-carboxamide,

(3S)-N-(2-{{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)-3-hydroxypyrrolidine-1-carboxamide,

N-(2-{{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)-4-hydroxypiperidine-1-carboxamide,

5 N-(2-{{[(2S)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)urea trifluoroacetate,

N-(2-{{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)urea trifluoroacetate,

10 N-(2-{{[(2S)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorophenyl)urea trifluoroacetate,

N-{{[(2-{{[(2S)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)amino]carbonyl}methanesulfonamide trifluoroacetate,

15 (4S)-2-(2-{{[(2S)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)isoxazolidin-4-ol trifluoroacetate,

(4R)-2-(2-{{[(2S)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)isoxazolidin-4-ol trifluoroacetate,

(4S)-2-(2-{{[(2S)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)-4-methylisoxazolidin-4-ol trifluoroacetate,

20 (4R)-2-(2-{{[(2S)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)-4-methylisoxazolidin-4-ol trifluoroacetate,

2-{{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-N-(methylsulfonyl)benzamide trifluoroacetate,

25 2-{{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-N-1H-tetrazol-5-ylbenzamide bis(trifluoroacetate),

3-{{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-{{[(3R)-3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenol bis(trifluoroacetate),

3-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-{{{(3S)-3-(dimethylamino)pyrrolidin-1-yl}carbonyl}phenol bis(trifluoroacetate),

(3S)-1-(5-chloro-2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)pyrrolidin-3-ol trifluoroacetate,

3-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-{{{(3S)-3-methoxypyrrolidin-1-yl}carbonyl}phenol trifluoroacetate,

3-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-{{{(2R)-2-(hydroxymethyl)pyrrolidin-1-yl}carbonyl}phenol trifluoroacetate,

3-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-{{{(2S)-2-(hydroxymethyl)pyrrolidin-1-yl}carbonyl}phenol trifluoroacetate,

3-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-{{{3-(hydroxymethyl)pyrrolidin-1-yl}carbonyl}phenol trifluoroacetate,

1-(2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)-D-prolinamide trifluoroacetate,

N-(4-hydroxy-2-{{{(2S)-2-hydroxy-3-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}phenyl)acetamide trifluoroacetate,

N-(4-hydroxy-2-{{{(2S)-2-hydroxy-3-(5-methyl-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}phenyl)acetamide trifluoroacetate,

N-(5-chloro-2-{{{(2S)-2-hydroxy-3-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}-4-methoxyphenyl)acetamide trifluoroacetate,

N-(5-chloro-4-hydroxy-2-{{{(2S)-2-hydroxy-3-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}phenyl)acetamide trifluoroacetate,

(3S)-N-(2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-methoxyphenyl)-3-hydroxypyrrolidine-1-carboxamide trifluoroacetate,

(3S)-N-(2-{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxyphenyl)-3-hydroxypyrrolidine-1-carboxamide trifluoroacetate,

(3S)-1-(4-hydroxy-2-{{(2S)-2-hydroxy-3-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}benzoyl)pyrrolidin-3-ol trifluoroacetate,

2-{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-5-methylbenzoic acid hydrochloride,

2-{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-methoxybenzoic acid hydrochloride,

(3S)-1-(2-{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-5-methylbenzoyl)pyrrolidin-3-ol trifluoroacetate,

(3S)-1-(2-{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-methoxybenzoyl)pyrrolidin-3-ol trifluoroacetate,

5-chloro-2-{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}benzoic acid hydrochloride,

(3S)-1-(5-chloro-2-{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}benzoyl)pyrrolidin-3-ol trifluoroacetate,

2-{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-5-fluorobenzoic acid hydrochloride,

(3S)-1-(2-{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-5-fluorobenzoyl)pyrrolidin-3-ol trifluoroacetate,

N-(2-{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}phenyl)pyrrolidine-1-carboxamide trifluoroacetate,

Methyl 4-(acetylamino)-3-{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}benzoate trifluoroacetate,

4-(acetylamino)-3-{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}benzoic acid trifluoroacetate,

N-(2-{{(2S)-3-(5-chloro-3'-fluoro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxyphenyl)acetamide,

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-(2-hydroxypropyl)benzamide,

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-(2-hydroxy-1,1-dimethylethyl)benzamide,

5 2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-N-cyclopentyl-4-hydroxybenzamide,

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-(2-methoxyethyl)benzamide,

10 2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-(2-hydroxyphenyl)benzamide,

N-(tert-butyl)-2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzamide,

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-(2-hydroxy-1-methylethyl)benzamide,

15 2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-isobutylbenzamide,

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-(4-hydroxycyclohexyl)benzamide,

20 2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-N-(2,3-dihydroxypropyl)-4-hydroxybenzamide,

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-(2-hydroxyethyl)-N-methylbenzamide,

Methyl *N*-(2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)serinate,

25 2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-N-(1-ethylpropyl)-4-hydroxybenzamide,

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-(tetrahydrofuran-2-ylmethyl)benzamide,

30 2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-[1-(hydroxymethyl)-2,2-dimethylpropyl]benzamide,

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-N-{{{(1S,2R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-yl}methyl}-4-hydroxybenzamide,

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-[1-(hydroxymethyl)-2-methylpropyl]benzamide,

3-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-{{[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}phenol,

3-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-{{[3-(hydroxymethyl)piperidin-1-yl]carbonyl}phenol,

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-N-[5-(1,1-dimethylpropyl)-2-hydroxyphenyl]-4-hydroxybenzamide,

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-[3-(1-hydroxyethyl)phenyl]benzamide,

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-N-(cyclopropylmethyl)-4-hydroxybenzamide,

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-pyrrolidin-1-ylbenzamide,

N-[(1R,4S)-bicyclo[2.2.1]hept-2-yl]-2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzamide,

4-(4-chlorophenyl)-1-(2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)piperidin-4-ol,

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-(2-hydroxy-1-phenylethyl)benzamide,

1-(2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)-4-phenylpiperidin-4-ol,

3-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-(3,4-dihydroisoquinolin-2(1H)-ylcarbonyl)phenol,

3-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-{{[2-(hydroxymethyl)piperidin-1-yl]carbonyl}phenol,

1-(2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)-N,N-dimethylprolinamide,

Methyl (4R)-1-(2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)-4-hydroxyprolinate,

5 (3R)-1-(2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)piperidin-3-ol,

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-(2-hydroxycyclohexyl)benzamide,

10 3-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-[(4-phenylpiperidin-1-yl)carbonyl]phenol,

3-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-(thiomorpholin-4-ylcarbonyl)phenol,

1-(2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)piperidin-3-ol,

15 2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-N-(cyclopropylmethyl)-4-hydroxy-N-propylbenzamide,

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N,N-diisobutylbenzamide,

20 3-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-(1,3-dihydro-2H-isoindol-2-ylcarbonyl)phenol,

N-(2-tert-butoxyethyl)-2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-isobutylbenzamide,

3-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-[(4-fluoropiperidin-1-yl)carbonyl]phenol,

25 3-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-[(4,4-difluoropiperidin-1-yl)carbonyl]phenol,

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-N-phenylbenzamide,

3-{{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-({[(2*R*)-2-[hydroxy(diphenyl)methyl]pyrrolidin-1-yl]carbonyl)phenol,

2-{{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-(2-hydroxyethyl)-*N*-methylbenzamide,

3-{{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-(pyrrolidin-1-ylcarbonyl)phenol,

3-{{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-{{[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}phenol,

3-{{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-{{[3-(hydroxymethyl)piperidin-1-yl]carbonyl}phenol,

4-(4-chlorophenyl)-1-(2-{{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)piperidin-4-ol,

3-{{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-{{[4-(hydroxymethyl)piperidin-1-yl]carbonyl}phenol,

1-(2-{{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)-4-phenylpiperidin-4-ol,

3-{{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-(3,4-dihydroisoquinolin-2(1*H*)-ylcarbonyl)phenol,

3-{{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-{{[2-(hydroxymethyl)piperidin-1-yl]carbonyl}phenol,

3-{{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-{{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenol,

1-(2-{{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)-*N,N*-dimethylprolinamide,

2-{{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-cyclohexyl-4-hydroxy-*N*-(2-hydroxyethyl)benzamide,

Methyl (4*R*)-1-(2-{{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)-4-hydroxyprolinate,

(3*R*)-1-(2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)piperidin-3-ol,

3-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-phenylpiperidin-1-yl)carbonyl]phenol,

5. 3-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-(thiomorpholin-4-ylcarbonyl)phenol,

1-(2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)piperidin-3-ol,

2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-(cyclopropylmethyl)-4-hydroxy-*N*-propylbenzamide,

10 2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N,N*-diisobutylbenzamide,

3-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-(1,3-dihydro-2*H*-isoindol-2-ylcarbonyl)phenol,

15 *N*-(2-*tert*-butoxyethyl)-2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-isobutylbenzamide,

3-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-fluoropiperidin-1-yl)carbonyl]phenol,

20 3-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4,4-difluoropiperidin-1-yl)carbonyl]phenol,

2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-(2-hydroxypropyl)benzamide,

2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-(2-hydroxy-1,1-dimethylethyl)benzamide,

25 2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-cyclopentyl-4-hydroxybenzamide,

2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-(2-methoxyethyl)benzamide,

30 2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-(2-hydroxyphenyl)benzamide,

2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-(2-hydroxy-1-methylethyl)benzamide,

2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-isobutylbenzamide,

5 2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-(2-hydroxyethyl)benzamide,

2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-(4-hydroxycyclohexyl)benzamide,

10 2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-(2,3-dihydroxypropyl)-4-hydroxybenzamide,

Methyl *N*-(2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)serinate,

2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-(1-ethylpropyl)-4-hydroxybenzamide,

15 2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-(tetrahydrofuran-2-ylmethyl)benzamide,

2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-[1-(hydroxymethyl)-2,2-dimethylpropyl]benzamide,

20 2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-[1-(hydroxymethyl)-2-methylpropyl]benzamide,

2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-[3-(1-hydroxyethyl)phenyl]benzamide,

2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-(cyclopropylmethyl)-4-hydroxybenzamide,

25 2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-pyrrolidin-1-ylbenzamide,

N-[(1*R*,4*S*)-bicyclo[2.2.1]hept-2-yl]-2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzamide,

30 2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-(2-hydroxy-1-phenylethyl)benzamide,

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-(2-hydroxycyclohexyl)benzamide,

1-(2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl}pyrrolidine-3-carboxamide trifluoroacetate,

5 1-(2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)-L-prolinamide trifluoroacetate,

2-chloro-5-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-{{{(3R)-3-(dimethylamino)pyrrolidin-1-yl}carbonyl}phenol bis(trifluoroacetate),

10 2-chloro-5-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-{{{(3R)-3-(hydroxymethyl)pyrrolidin-1-yl}carbonyl}phenol trifluoroacetate,

2-chloro-5-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-{{{(3S)-3-(hydroxymethyl)pyrrolidin-1-yl}carbonyl}phenol trifluoroacetate,

15 2-chloro-5-{{{(2S)-3-(5-fluoro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-(pyrrolidin-1-ylcarbonyl)phenol trifluoroacetate,

N-(2-{{{(2R)-3-(5-Fluoro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-methoxyphenyl)acetamide,

20 Methyl 2-{{{(2S)-3-(5-fluoro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}benzoate,

2-{{{(2S)-3-(5-Fluoro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}benzoic acid (hydrochloride),

(3S)-1-(2-{{{(2S)-3-(5-Fluoro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}benzoyl)pyrrolidin-3-ol,

25 3-{{{(2S)-3-(5-Fluoro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-(pyrrolidin-1-ylcarbonyl)phenol,

N-(4-fluoro-2-{{{(2S)-3-(5-fluoro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}phenyl)acetamide,

N-{5-chloro-2-[3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl}cyclopentanecarboxamide,

N-{5-chloro-2-[3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl}cyclopentanecarboxamide,

5 *N*-{5-chloro-4-hydroxy-2-[2-hydroxy-3-(1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]phenyl}cyclopentanecarboxamide,

N-(5-Chloro-2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxyphenyl)benzamide trifluoroacetate,

10 *N*-(5-Chloro-2-{{{(2*S*)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxyphenyl)benzamide trifluoroacetate,

N-(5-Chloro-2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxyphenyl)urea trifluoroacetate,

N-(5-Chloro-2-{{{(2*S*)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxyphenyl)urea trifluoroacetate,

15 *N*-(5-chloro-2-{{{(2*S*)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}phenyl)urea,

N-(5-chloro-2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}phenyl)urea,

20 *N*-(2-{{{(2*S*)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}phenyl)urea,

N-(2-{{{(2*S*)-2-hydroxy-3-(1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}phenyl)urea,

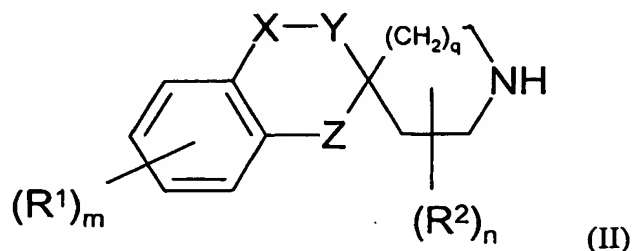
N-(4-fluoro-2-{{{(2*S*)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}phenyl)urea,

25 *N*-(4-fluoro-2-{{{(2*S*)-2-hydroxy-3-(1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}phenyl)urea,

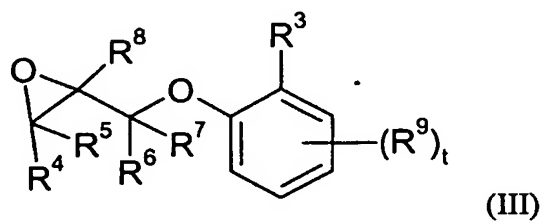
and pharmaceutically acceptable salts and solvates of any one thereof.

The present invention further provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined above which comprises,

(a) reacting a compound of formula

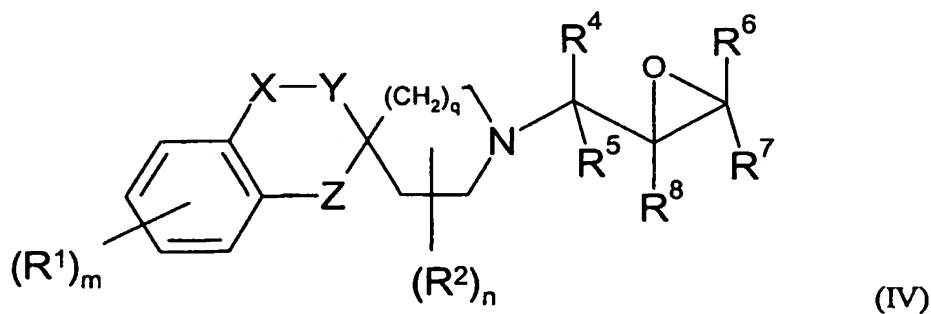


wherein m , R^1 , n , R^2 , q , X , Y and Z are as defined in formula (I), with a compound of formula



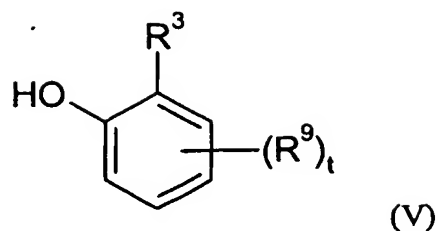
wherein R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , t and R^9 are as defined in formula (I); or

(b) reacting a compound of formula



wherein m , R^1 , n , R^2 , q , X , Y , Z , R^4 , R^5 , R^6 , R^7 and R^8 are as defined in formula (I), with a compound of formula

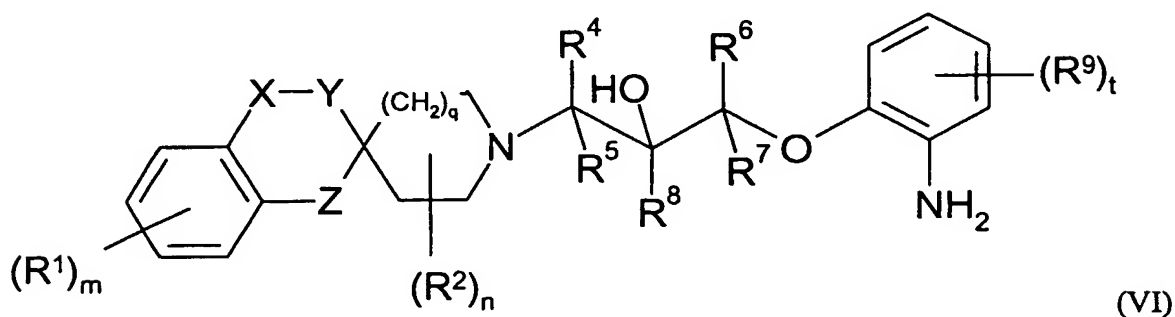
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wherein R^3 , t and R^9 are as defined in formula (I), in the presence of a suitable base; or

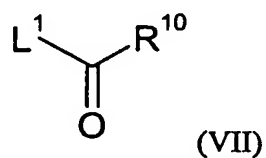
(c) when R^3 represents $-NHC(O)R^{10}$, reacting a compound of formula

5



wherein m , R^1 , n , R^2 , q , X , Y , Z , R^4 , R^5 , R^6 , R^7 , R^8 , t and R^9 are as defined in formula (I), with a compound of formula

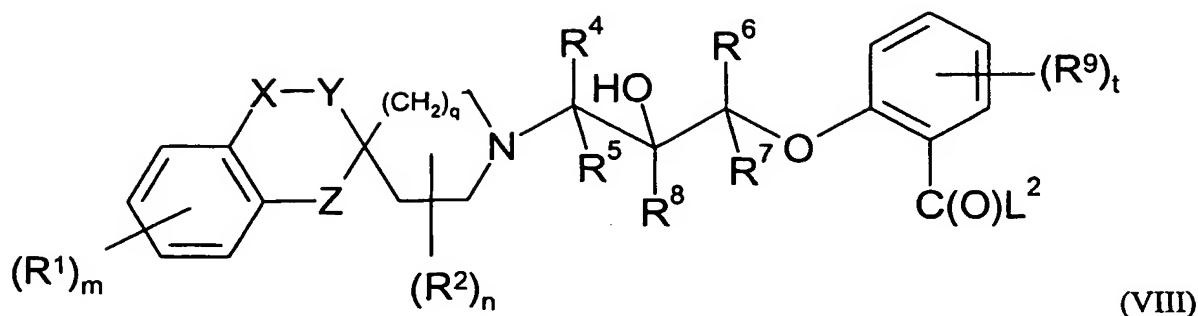
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wherein L^1 represents a leaving group (e.g. a hydroxyl group or a halogen atom such as chlorine) and R^{10} is as defined in formula (I); or

(d) when R^3 represents $-C(O)NR^{11}R^{12}$, reacting a compound of formula

15



wherein L^2 represents a leaving group (e.g. a hydroxyl group or a halogen atom such as chlorine) and m , R^1 , n , R^2 , q , X , Y , Z , R^4 , R^5 , R^6 , R^7 , R^8 , t and R^9 are as defined in

5 formula (I), with a compound of formula (IX), $NHR^{11}R^{12}$, wherein R^{11} and R^{12} are as defined in formula (I); or

(e) when R^3 represents $-NHC(O)R^{10}$, R^{10} represents $-NR^{14}R^{15}$ and R^{14} and R^{15} both represent hydrogen, reacting a compound of formula (VI) as defined in (c) above with potassium cyanate;

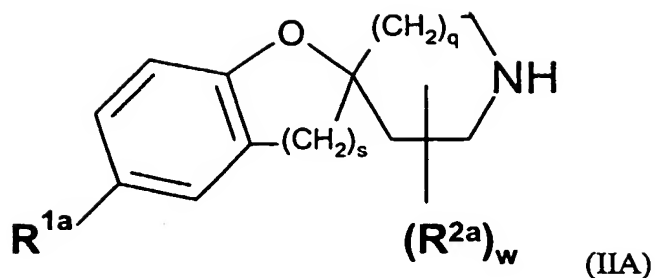
10

and optionally after (a), (b), (c), (d) or (e) forming a pharmaceutically acceptable salt or solvate.

The processes of the invention may conveniently be carried out in a solvent, e.g. an organic
 15 solvent such as an alcohol (e.g. methanol or ethanol), a hydrocarbon (e.g. toluene) or tetrahydrofuran, dimethylformamide, N-methylpyrrolidinone or acetonitrile at a temperature of, for example, 0°C or above such as a temperature in the range from 0, 5, 10, 15 or 20°C to 100, 110 or 120°C .

20 Certain compounds of formula (II) are novel. Thus, the present invention further provides an intermediate compound of formula

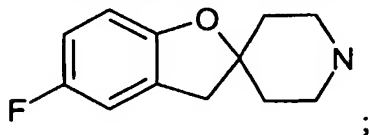
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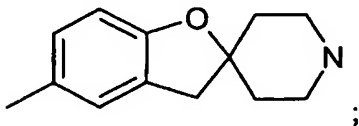
wherein R^{1a} is selected from fluorine, chlorine, methyl and trifluoromethyl; s is 1 or 2; q is 0 or 1; w is 0 or 1; and R^{2a} is fluorine.

5 Specific examples of compounds of formula (IIA) include:

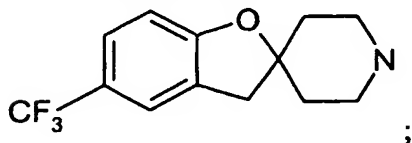
5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine]



10 5-methyl-3*H*-spiro[1-benzofuran-2,4'-piperidine]

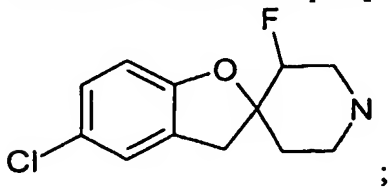


5-(trifluoromethyl)-3*H*-spiro[1-benzofuran-2,4'-piperidine]

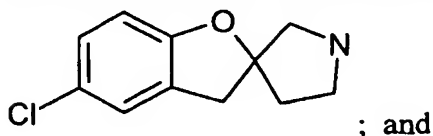


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5-chloro-3'-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine]

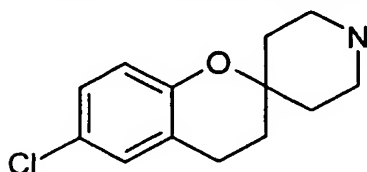


5-chloro-3*H*-spiro[1-benzofuran-2,3'-pyrrolidine]



; and

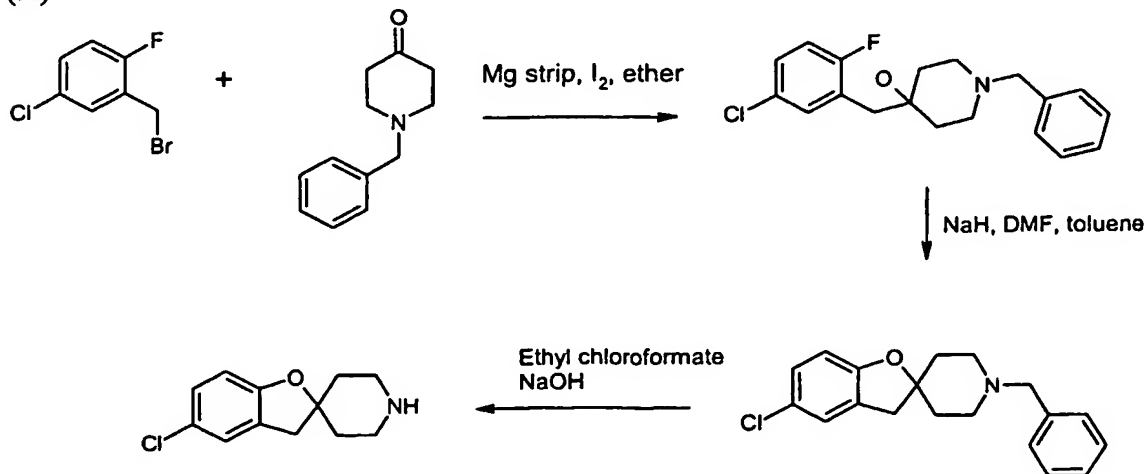
6-chloro-3,4-dihydrospiro[chromene-2,4'-piperidine]



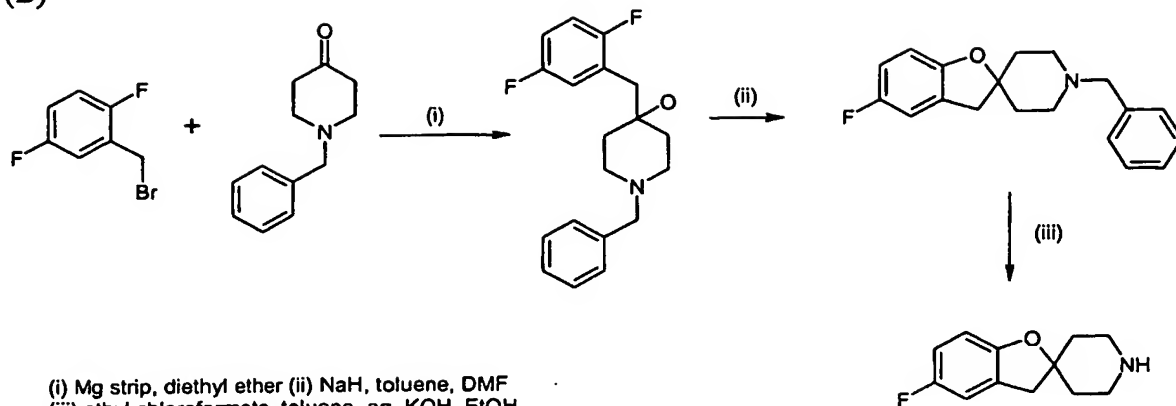
Other compounds of formula (II) and compounds of formulae (III), (IV), (V), (VI), (VII), (VIII) and (IX) are either commercially available, are known in the literature or may be prepared using known techniques.

For example, compounds of formula (II) in which *m* is 1, R^1 is chlorine or fluorine, *n* is 0, *q* is 1, one of *X* and *Y* represents a bond and the other of *X* and *Y* represents an oxygen atom and *Z* represents CH_2 , may be prepared according to the following reaction schemes in which DMF denotes dimethylformamide, EtOH denotes ethanol, DME denotes 1,2-dimethoxyethane, *i*-Pr denotes isopropyl, THF denotes tetrahydrofuran, KO*t*Bu denotes potassium *tert* butoxide and HOAc denotes acetic acid.:

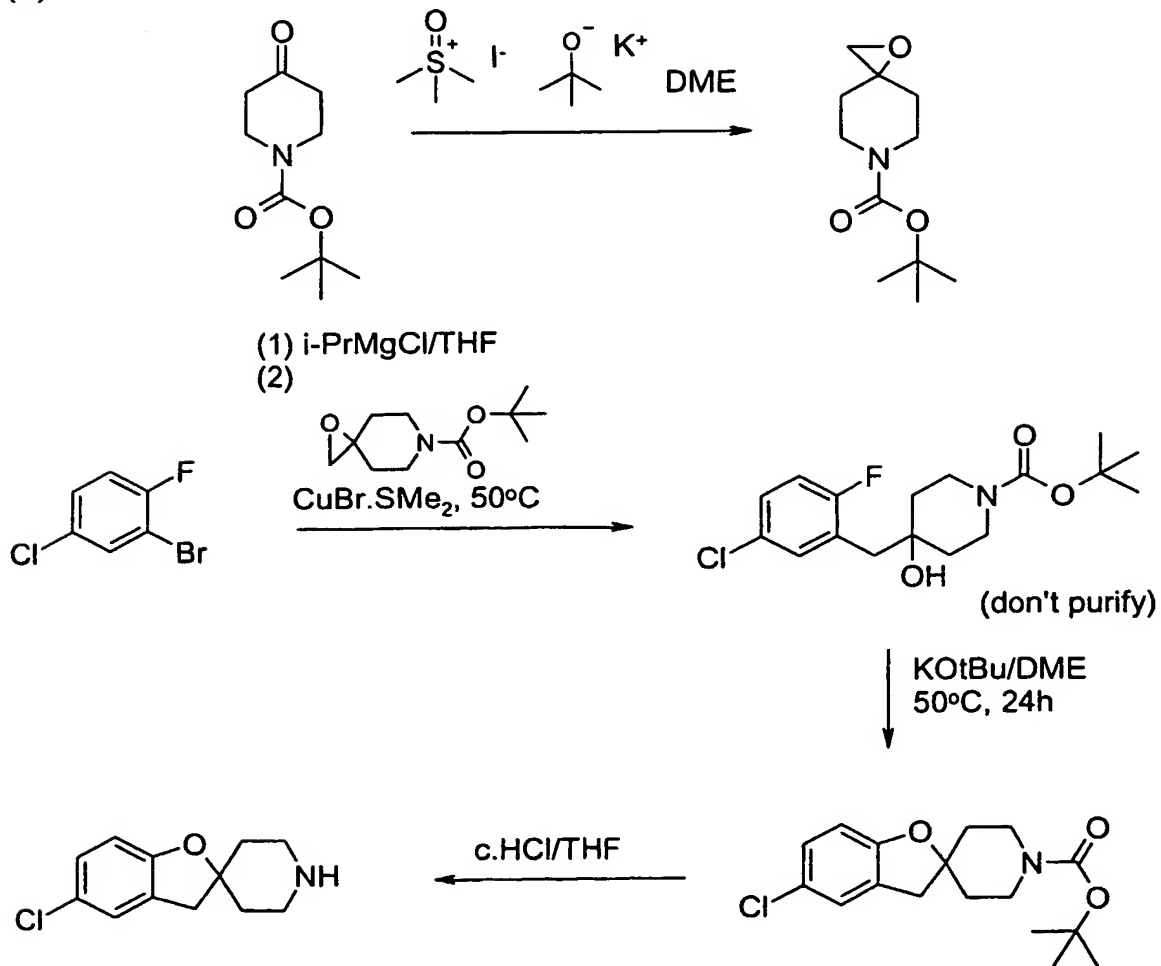
(A)



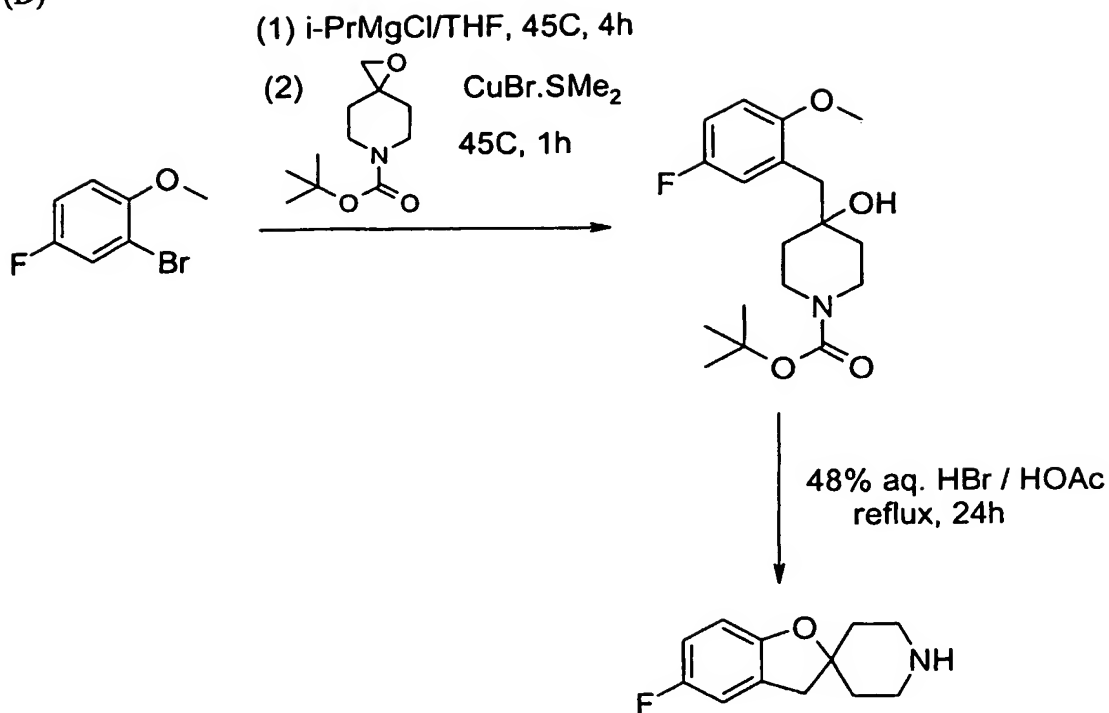
(B)



5 (C)



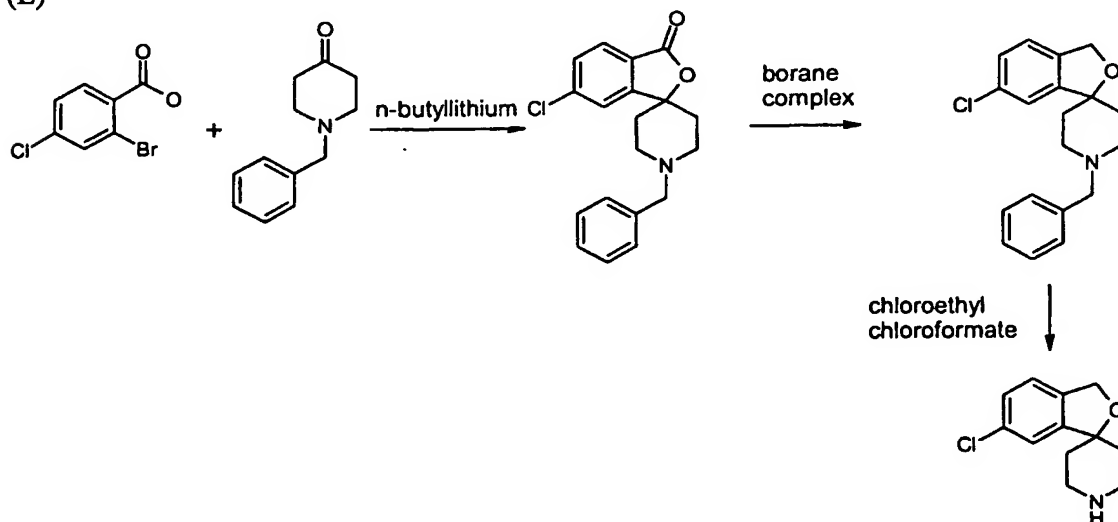
(D)

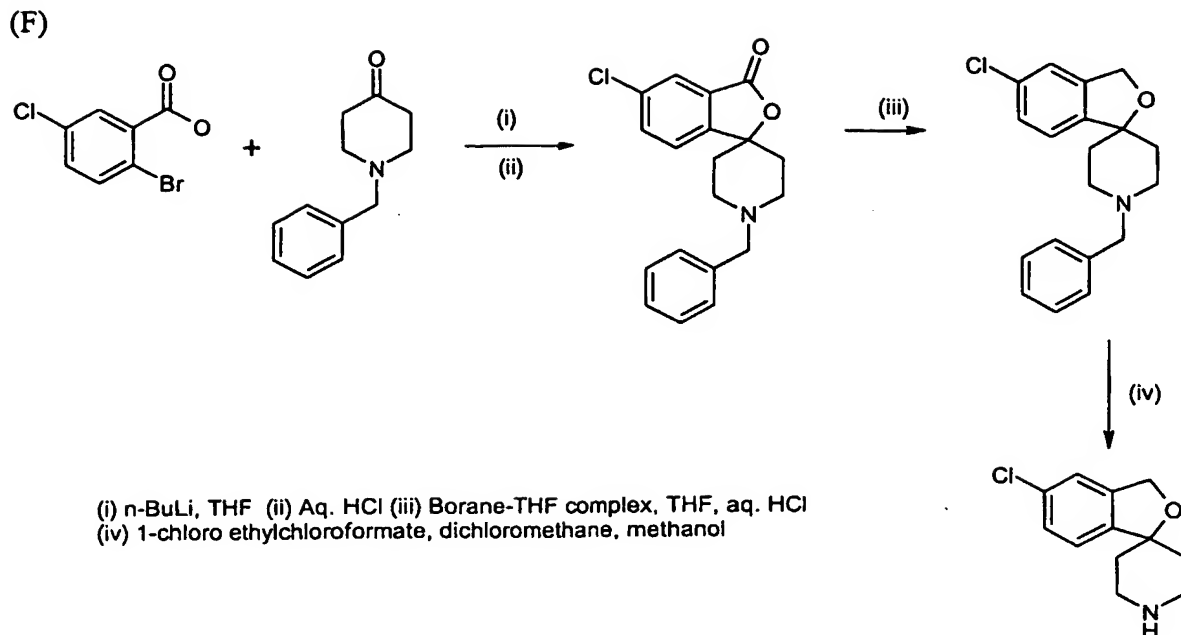


Compounds of formula (II) in which m is 1, R^1 is chlorine, n is 0, q is 1, X represents CH_2 ,

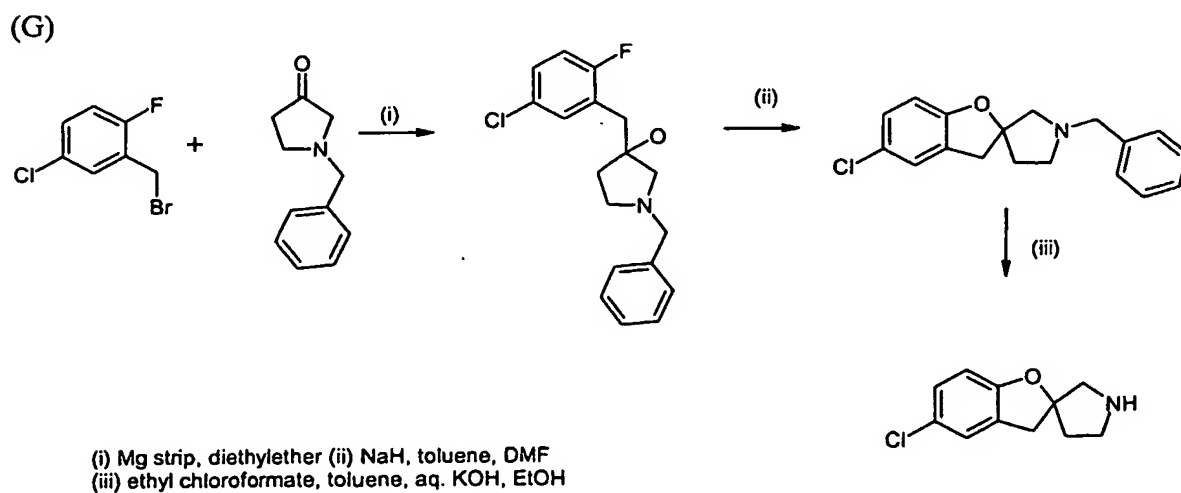
5 Y represents an oxygen atom and Z represents a bond, may be prepared according to the following reaction schemes in which THF denotes tetrahydrofuran:

(E)



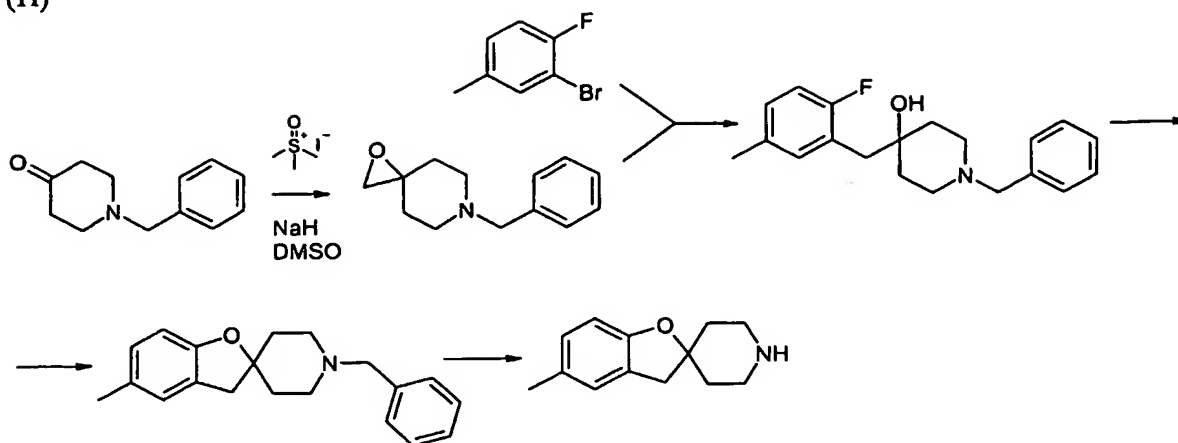


Compounds of formula (II) in which m is 1, R¹ is chlorine, n is 0, q is 0, one of X and Y represents a bond and the other of X and Y represents an oxygen atom and Z represents CH₂, may be prepared according to the following reaction scheme in which DMF denotes dimethylformamide and EtOH denotes ethanol:



Compounds of formula (II) in which m is 1, R¹ is methyl, n is 0, q is 1, one of X and Y represents a bond and the other of X and Y represents an oxygen atom and Z represents CH₂, may be prepared according to the following reaction scheme in which DMSO denotes dimethylsulphoxide:

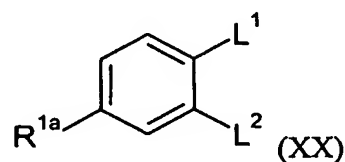
(H)



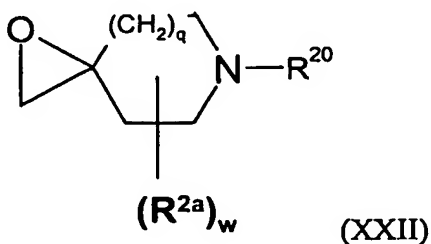
Process routes (C), (D) and (H) above are novel.

5

Thus, the present invention further provides a process for preparing a compound of formula (IIA) as defined above in which s is 1, which comprises reacting a compound of formula

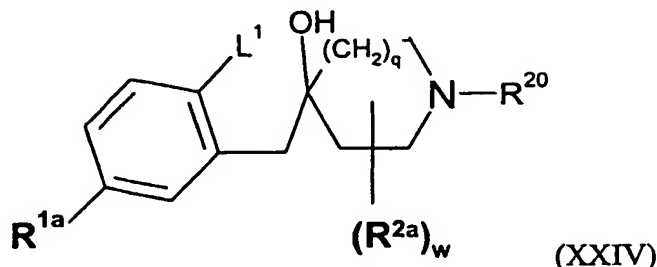


- 10 wherein L^1 represents a suitable leaving group (e.g. an electron withdrawing group such as a halogen atom) or an alkoxy, particularly methoxy, group, L^2 represents a suitable leaving group such as a halogen atom and R^{1a} is as defined in formula (IIA), with a compound of formula



- 15 wherein R^{20} represents a protecting group such as a benzyl group or a group $-C(O)-O-R^{21}$ in which R^{21} represents an alkyl (e.g. C_1 - C_6 alkyl, particularly *tert*-butyl) or aryl (e.g.

phenyl) group and q , w and R^{2a} are as defined in formula (IIA) to form a compound of formula



followed by a cyclisation reaction and then removal of the protecting group R^{20} .

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the reagents may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999).

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

Compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers (including atropisomers) of the compounds of formula (I) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention. Enantiomerically pure forms are particularly desired.

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially MIP-1 α chemokine receptor) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative and hyperproliferative diseases and immunologically-mediated diseases including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS).

Examples of these conditions are:

(1) **(the respiratory tract)** airways diseases including chronic obstructive pulmonary

disease (COPD) such as irreversible COPD; asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

(2) **(bone and joints)** rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin)** psoriasis, atopic dermatitis, contact dermatitis and other eczematous dermatides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

(5) **(other tissues and systemic disease)** multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia pupura;

(6) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(7) cancers, especially non-small cell lung cancer (NSCLC) and squamous sarcoma;

(8) diseases in which angiogenesis is associated with raised chemokine levels; and

(9) cystic fibrosis, stroke, re-perfusion injury in the heart, brain, peripheral limbs and sepsis.

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention also provides a method of treating an inflammatory disease which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

5

The invention still further provides a method of treating an airways disease which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

10

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of formula (I) may be in the range from 0.001 mg/kg to 30 mg/kg.

15

The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

20 Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

25 The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical
30 composition of the invention which comprises mixing a compound of formula (I), or a

pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the skin or to the lung and/or airways) in the form, e.g., of creams, solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of solutions or suspensions; or by subcutaneous administration; or by rectal administration in the form of suppositories; or transdermally.

The invention will now be further explained by reference to the following illustrative examples, in which ^1H NMR spectra were recorded on Varian Unity Inova 400. The central solvent peak of chloroform- d (δ_{H} 7.27 ppm), acetone- d_6 (δ_{H} 2.05 ppm), DMSO- d_6 (δ_{H} 2.50 ppm), or methanol- d_4 (δ_{H} 4.87 ppm) were used as internal standard. Low resolution mass spectra and accurate mass determination were recorded on a Hewlett-Packard 1100 LC-MS system equipped with APCI /ESI ionisation chambers.

All solvents and commercial reagents were laboratory grade and used as received.

The nomenclature used for the compounds was generated with ACD/IUPAC Name Pro.

The abbreviations or terms used in the examples have the following meanings:

BuLi	: butyllithium
DCM	: dichloromethane
DEAD	: diethyl azodicarboxylate
DMAP	: 4-dimethylaminopyridine
DME	: 1,2-dimethoxyethane
DMF	: <i>N,N</i> -dimethylformamide
DMSO	: dimethyl sulfoxide
Et ₂ O	: diethyl ether
EtOAc	: ethyl acetate
EtOH	: ethanol
HOAc	: acetic acid

KotBu : potassium *tert* butoxide
 MeCN : acetonitrile
 MeOH : methanol
 NMP : 1-methyl-2-pyrrolidinone
 5 TEA : triethylamine
 TFA : trifluoroacetic acid
 THF : tetrahydrofuran
 TMSCl : chlorotrimethylsilane

10 SELECTFLUOR™ fluorinating reagent (Aldrich)

Chemical name: [1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane
 bis(tetrafluoroborate)]

PS-Carbodiimide : a resin-bound coupling agent

15 Chemical name: N-cyclohexylcarbodiimide-N'-propyloxymethyl polystyrene

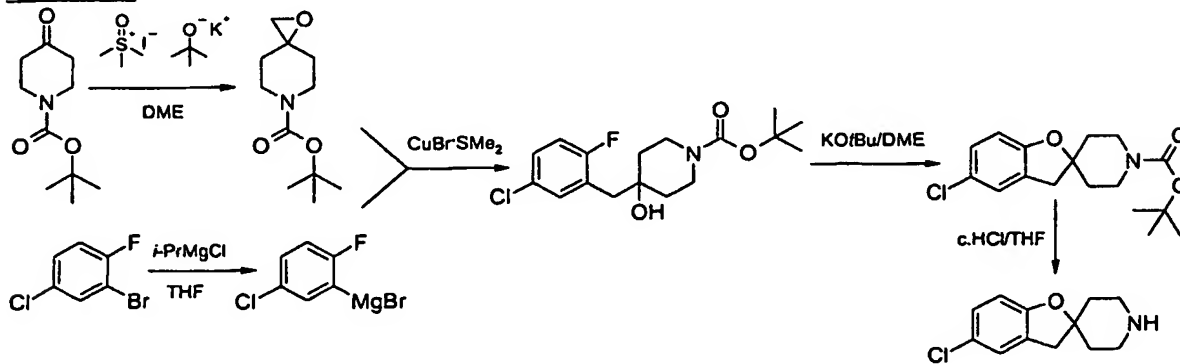
Examples

Intermediate compound: 5-Chloro-3H-spiro[1-benzofuran-2,4'-piperidine]

Method A: This compound was prepared as described by Effland, R. C; Gardner, B. A;

20 Strupczewski, J., *J. Heterocyclic Chem.*, 1981, 18, 811-814.

Method B:



i) 1-Oxa-6-azaspiro[2.5]octane-6-carboxylic acid, 1,1-dimethylethyl ester

Potassium *t*-butoxide (31g) was added to a stirred suspension of trimethylsulfoxonium iodide (60.8g) in 1,2-dimethoxyethane (250ml) at 20°C. After 1 hour, the mixture was added portionwise over 30 minutes to a stirred solution of 4-oxo-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester (50g) in 1,2-dimethoxyethane (50ml) at 0°C. After a further 2
5 hours, water (500ml) was added and the mixture extracted with *tert*.-butyl methyl ether (2 × 500ml). The organic extracts were washed separately with saturated sodium bicarbonate solution (250ml), combined, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residual oil was co-evaporated with toluene (100ml) to give the sub-title compound (43.25g, 81 %) as a solid.

10 ¹H-NMR (400 MHz, CDCl₃): δ 1.46 (9H, s), 1.43-1.48 (2H, m), 1.75-1.84 (2H, m), 2.69 (2H, s), 3.38-3.47 (2H, m), 3.70-3.75 (2H, m).

(ii) 5-Chlorospiro[1-benzofuran-2,4'-piperidine]-1'-carboxylic acid, 1,1-dimethyl ester

15 A solution of iso-propylmagnesium chloride in tetrahydrofuran (2M, 106.6ml) was added dropwise over 15 minutes to a stirred solution of 2-bromo-4-chloro-1-fluorobenzene (42.5g) in anhydrous tetrahydrofuran (250ml) at 0°C under nitrogen. After a further 15 minutes; a solution of 1-oxa-6-azaspiro[2.5]octane-6-carboxylic acid, 1,1-dimethylethyl ester (43.2g) in anhydrous tetrahydrofuran (50ml) was added followed by

20 copper(I)bromide dimethyl sulphide complex (0.4g). The mixture was stirred at 40°C for 18 hours, cooled to 20°C, diluted with water (300ml) and extracted with *tert*.-butyl methyl ether (2 × 300ml). Organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residual oil was dissolved in 1,2-dimethoxypropane (200ml). Potassium *tert*.-butoxide (22.8g) was added and the

25 mixture stirred at 40°C for 16 hours then at 50°C for 24 hours. Further potassium *tert*.-butoxide (5.7g) was added and stirring continued at 50°C for 2 hours then at 55°C for 4 hours. Water (500ml) was added and the mixture extracted with *tert*.-butyl methyl ether (2 × 300ml). Organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give the sub-title compound (47.45g, 67 %) as an oil.

30 ¹H-NMR (400 MHz, CDCl₃): δ 1.47 (9h, s), 1.67 (2H, td), 1.85-1.93 (2H, m), 2.94 (2H, s), 3.39 (2H, td), 3.65-3.80 (2H, m), 6.67 (1H, d), 7.06 (1H, d), 7.10 (1H, s).

iii) 5-Chlorospiro[1-benzofuran-2,4'-piperidine]

Concentrated hydrochloric acid (23ml) was added to a solution of 5-chlorospiro[1-benzofuran-2,4'-piperidine]-1'-carboxylic acid, 1,1-dimethyl ester (46.43g) in tetrahydrofuran (230ml). The mixture was stirred at 50°C for 6 hours, cooled to 20°C, diluted with water (230ml) and extracted with *tert.*-butyl methyl ether (2 × 230ml). The aqueous phase was adjusted to pH >10 by addition of 50wt.% sodium hydroxide solution and extracted with *tert.*-butyl methyl ether (3 × 300ml). Organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residual oil was dissolved in tetrahydrofuran (240ml), concentrated hydrochloric acid (12ml) was added and the mixture stirred at 20°C for 16 hours. Precipitated solid was filtered and dissolved in water (100ml). The solution was adjusted to pH >10 by addition of 50wt.% sodium hydroxide solution and extracted with *tert.*-butyl methyl ether (3 × 100ml) to give the title compound (13.3g, 45 %) as a solid.

¹H-NMR (400 MHz, CDCl₃): δ 1.69-1.76 (2H, m), 1.83-1.87 (2H, m), 2.78-2.84 (2H, m), 2.98-3.03 (4H, m), 6.65 (1H, d), 7.04 (1H, d), 7.13 (1H, s).

APCI-MS: m/z 224/6 [M+H]⁺

Intermediate compound: 5-Fluoro-3H-spiro[1-benzofuran-2,4'-piperidine]**Method A:****i) 1'-Benzyl-5-fluoro-3H-spiro[1-benzofuran-2,4'-piperidine]**

To a stirring suspension of magnesium strip (763 mg) in diethyl ether (7 mL) was added a crystal of iodine followed by (0.4 mL of 2-(bromomethyl)-1,4-difluorobenzene under nitrogen. The reaction mixture was initiated with a high intensity heat gun, 2-(bromomethyl)-1,4-difluorobenzene 5.0 g, 24.25 mmol) in diethyl ether (7 mL) was added slowly maintaining gentle reflux. After addition was completed the reaction mixture was stirred at reflux for 100 min, cooled to room temperature. To this reaction mixture a solution of 1-benzylpiperidin-4-one (4.57 g, 24.25 mmol) in diethyl ether (12 mL) was added dropwise with vigorous stirring. After addition was completed the reaction mixture was left at room temperature overnight. Aqueous NH₄Cl solution was added and stirred at

room temperature until hydrolysis was completed, extracted with diethyl ether. The organic layer was washed with H₂O, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.2% NH₄OH) to give intermediate 1-benzyl-4-(2,5-

5 difluorobenzyl)piperidin-4-ol (2.74 g) containing large quantities of unknown impurities. To a suspension of NaH (55%, 1.12 g, 26.0 mmol) in toluene (10 mL) was slowly added a solution of 1-benzyl-4-(2,5-difluorobenzyl)piperidin-4-ol in toluene (15 mL). After addition was completed the reaction mixture was stirred at 110 °C (in a pre heated oil bath), after 5 min, DMF (9 mL) was added and stirring was continued at reflux
10 temperature for 2h. The reaction mixture was cooled to room temperature, H₂O (20 mL) was added and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH₄OH) to give the subtitled compound (190 mg).

15 ¹H-NMR (CDCl₃, 400 MHz): δ 7.39-7.26 (m, 5H); 6.88-6.76 (m, 2H); 6.67 (dd, *J* = 4.2, 8.7 Hz, 1H); 3.59 (s, 2H); 2.99 (s, 2H); 2.68-2.47 (m, 4H); 2.03-1.94 (m, 2H); 1.86-1.76 (m, 2H).

APCI-MS: *m/z* 298(MH⁺).

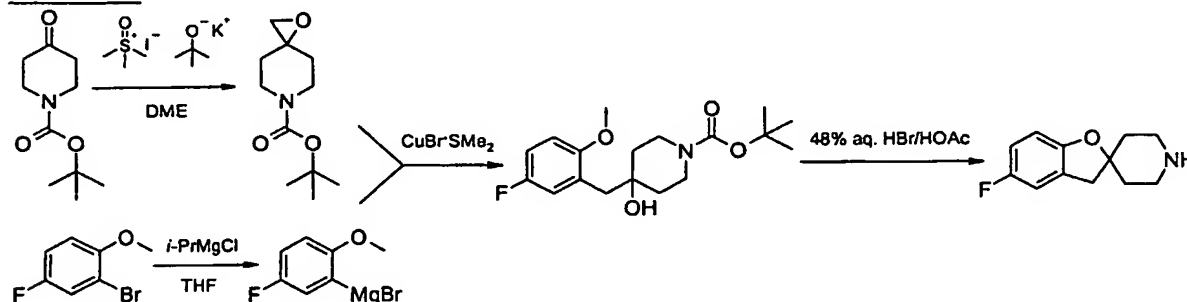
20 (ii) 5-Fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine]

Ethyl chloroformate (65.6 mg, 0.604 mmol) was added to a solution of 1'-benzyl-5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidin] (150 mg, 0.504 mmol) in toluene (2 mL) and the reaction mixture was refluxed overnight. The reaction mixture was cooled to room temperature, diluted by addition of toluene, washed successively with aqueous NaHCO₃
25 and H₂O. The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was dissolved in ethanol (3.5 mL), aqueous KOH (800 mg, KOH in 0.8 mL H₂O) was added and the reaction mixture was stirred at reflux temperature overnight, cooled to room temperature, ethanol was removed in vacuo. Aqueous layer was extracted with Et₂O, combined ether layer was washed with 3N aqueous HCl. Combined aqueous
30 layer was made pH 10 by addition of aqueous NaOH. The basic solution was extracted

with ethyl acetate. The combined organic layer was washed with H₂O, dried over Na₂SO₄, filtered and concentrated. The residue was purified by HPLC (10-55% CH₃CN in H₂O, 0.1% NH₄OH) to give the titled compound (49 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 6.92-6.87 (m, 1H); 6.81-6.75 (m, 1H); 6.64 (dd, *J* = 4.2, 8.7 Hz, 1H); 3.08-2.98 (m, 4H); 2.89-2.81 (m, 2H); 1.91-1.83 (m, 2H); 1.78-1.71 (m, 2H).
APCI-MS: *m/z* 208(MH⁺).

Method B:



(i) 4-[(5-Fluoro-2-methoxyphenyl)methyl]-4-hydroxy-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester.

A solution of iso-propylmagnesium chloride in tetrahydrofuran (2M, 130ml) was added dropwise over 30 minutes to a stirred solution of 2-bromo-4-fluoroanisole (34.2ml) in anhydrous tetrahydrofuran (400ml) at 30°C under nitrogen. After a further 16 hours at 30°C, copper(I)bromide dimethyl sulphide complex (0.4g) was added followed by a solution of 1-oxa-6-azaspiro[2.5]octane-6-carboxylic acid, 1,1-dimethylethyl ester (56.2g) in anhydrous tetrahydrofuran (110ml). After a further 3 hours at 30°C, the solution was cooled to 20°C, diluted with water (600ml) and extracted with *tert.*-butyl methyl ether (600ml) then ethyl acetate (600ml). Combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give crude sub-title compound (86 g) as a solid.

APCI-MS: *m/z* 240 [M+H-(CH₃)₂CCH₂-CO₂]⁺

(ii) 5-Fluorospiro[1-benzofuran-2,4'-piperidine] hydrochloride

Hydrobromic acid (48%, 60ml) was added to a solution of the crude 4-[(5-Fluoro-2-methoxyphenyl)methyl]-4-hydroxy-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester in acetic acid (300ml). The mixture was heated at reflux for 5 hours. Further hydrobromic acid (48%, 60ml) was added and reflux continued for 24 hours. The mixture was cooled to room temperature, added to water (2 l) and extracted with *tert.*-butyl methyl ether (2 × 500ml). The aqueous phase was adjusted to pH > 10 by addition of 50 wt.% sodium hydroxide solution and extracted with *tert.*-butyl methyl ether (2 l + 1 l). Organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residual oil was dissolved in tetrahydrofuran (200ml), concentrated hydrochloric acid (13 ml) was added and the solution evaporated under reduced pressure. The residual solid was crystallised from tetrahydrofuran / *tert.*-butyl methyl ether (4:1, 500 ml) to give the title compound (20.0 g, overall yield 31 %).

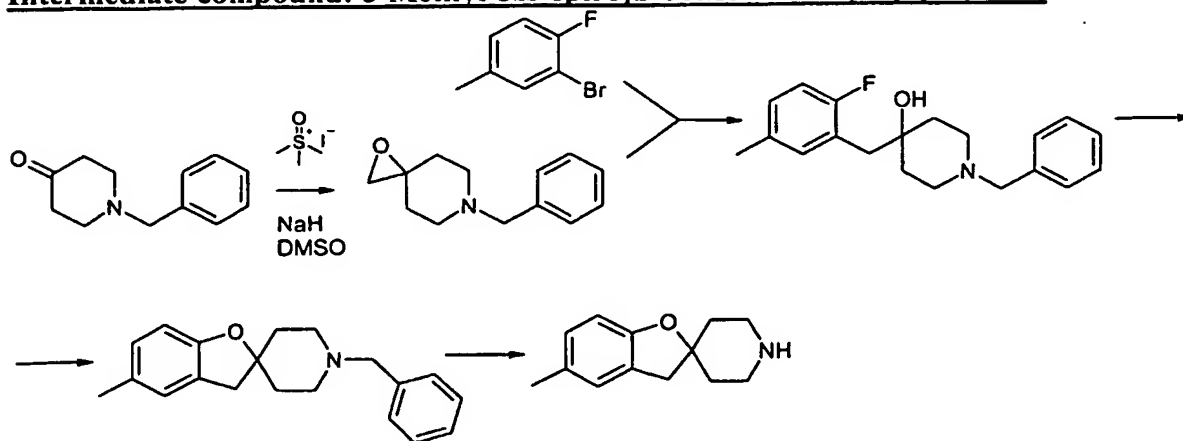
¹H-NMR (CD₃OD, 400 MHz): δ 1.86-1.98 (2H, m), 2.03-2.07 (2H, m), 3.05 (2H, s), 3.16-3.27 (4H, m), 6.61 (1H, dd), 6.74 (1H, dt), 6.81 (1H, dd).

APCI-MS: m/z 208 [M+H]⁺

Intermediate compound: 3H-Spiro[1-benzofuran-2,4'-piperidine]

This compound was prepared as described by Effland, R. C; Gardner, B. A; Strupczewski, J., *J. Heterocyclic Chem.*, **1981**, *18*, 811-814.

Intermediate compound: 5-Methyl-3H-spiro[1-benzofuran-2,4'-piperidine]



(i) 6-benzyl-1-oxa-6-azaspiro[2.5]octane

Sodium hydride (55 % suspension in mineral oil, 1.57 g, 35 mmol) was washed with heptane, dried in the stream of nitrogen and suspended in dry DMSO (10 ml). A solution of trimethylsulfoxonium iodide (4.8 g, 22 mmol) in DMSO (45 ml) was added dropwise under nitrogen. After stirring for 20 min a solution of 1-benzylpiperidin-4-one (3.78 g, 20 mmol) was added dropwise. The mixture was stirred overnight at room temperature, then poured over ice (200 g), and extracted with dichloromethane (2 x 200 ml). The combined extracts were washed with water (3 x 100 ml) and dried over Na₂SO₄. The solvent was removed i. vacuo. The residue was dissolved in diethyl ether, and the insoluble material was removed by filtration. Evaporation of solvent afforded pale-yellow oil (2.95 g, 73 %).

¹H-NMR (CDCl₃, 400 MHz): δ 7.2 – 7.4 (m, 5H); 3.57 (s, 2H); 2.5 – 2.7 (m, 4H); 1.85 (m, 2H); 1.55 (m, 2H).

(ii) 1-benzyl-4-(2-fluoro-5-methylbenzyl)piperidin-4-ol

To a solution of 2-bromo-1-fluoro-4-methylbenzene (0.76 g, 4 mmol) in THF (15 ml) at –70 °C under Ar a solution of n-BuLi (1.6 M in hexane, 2.5 ml, 4 mmol) was added dropwise. The reaction mixture was stirred at –70 °C for 1 h, then BF₃•Et₂O (0.5 ml, 4 mmol) was added. After stirring for 20 min at –70 °C, a solution of 6-benzyl-1-oxa-6-azaspiro[2.5]octane (0.41 g, 2 mmol) in dry THF (5 ml) was added dropwise. The stirring was continued for 2 h at –70 °C, then the reaction mixture was quenched with sat. aq. NH₄Cl (20 ml). The layers were separated, the aqueous layer extracted with THF. The combined organic layers were dried over Na₂SO₄. The solvent was removed in vacuo. Diethyl ether (50 ml) was added to the residue, followed by a 2 M HCl in Et₂O (5 ml). The precipitate was collected, washed with Et₂O, and dissolved in minimal volume of methanol (ca. 5 ml). Water (50 ml) was added, and pH adjusted to 10 by addition of 2 M aq. NaOH. The mixture was extracted with ethyl acetate (2 x 25 ml), and the combined organic extracts were dried with Na₂SO₄. Evaporation of solvent afforded brownish oil.

APCI-MS: m/z 314 [M+H]⁺

(iii) 1'-benzyl-5-methyl-3H-spiro[1-benzofuran-2,4'-piperidine]

To a suspension of NaH (55% in mineral oil, 200 mg, 5 mmol) in toluene (10 mL) was slowly added a solution of crude 1-benzyl-4-(2-fluoro-5-methylbenzyl)piperidin-4-ol in toluene (15 mL). After addition was completed, the reaction mixture was heated to 110 °C and stirred for 5 min. DMF (9 mL) was added and stirring was continued at reflux temperature for 10 h. The reaction mixture was cooled to room temperature, poured into water (50 ml), and extracted with ethyl acetate (2 x 25 ml). The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (ethyl acetate / n-heptane) to give the subtitle compound (240 mg, 41 %).
¹H-NMR (CDCl₃, 400 MHz): δ 7.2 – 7.4 (m, 5H); 6.8 – 6.9 (m, 2H); 6.64 (d, *J* = 10.8 Hz, 1 H), 3.54 (s, 2H); 2.91 (s, 2H); 2.4 – 2.7 (m, 4H); 2.24 (s, 3H); 1.92 (m, 2H); 1.78 (m, 2H).

APCI-MS: *m/z* 294 [M+H]⁺

(iv) 5-methyl-3*H*-spiro[1-benzofuran-2,4'-piperidine]

To a solution of 1'-benzyl-5-methyl-3*H*-spiro[1-benzofuran-2,4'-piperidine] (0.12 g, 0.41 mmol) in dichloromethane (3 ml) was added 1-chloroethyl chloroformate (87 mg, 0.61 mmol). The solution was stirred at room temperature overnight. The solvent was removed i. vacuo. The residue was dissolved in methanol (3 ml), and the solution was heated at 70 °C for 2 h. The solvent was evaporated, and the residue treated with diethyl ether. The precipitate formed was collected by filtration, washed with diethyl ether, and dissolved in methanol (1 ml). Water (25 ml) was added, and pH was adjusted to 10 by addition of 2 M aq. NaOH. The mixture was extracted with dichloromethane (2 x 25 ml), and the combined organic extracts were dried over Na₂SO₄. Evaporation of solvent afforded brownish oil (64 mg, 77 %).

¹H-NMR (CDCl₃, 400 MHz): δ 6.95 (s, 1H); 6.90 (d, *J* = 8 Hz, 1 H); 6.64 (d, *J* = 8 Hz, 1 H); 3.11 (m, 2H); 2.95 (s, 2H); 2.85 (m, 2H); 2.26 (s, 3H); 1.88 (m, 2H); 1.72 (m, 2H).

APCI-MS: *m/z* 204 [M+H]⁺

Intermediate compound: 5-(Trifluoromethyl)-3*H*-spiro[1-benzofuran-2,4'-piperidine]

(i) 1-Benzyl-4-[2-fluoro-5-(trifluoromethyl)benzyl]piperidin-4-ol

To a stirring suspension of Mg strips (308 mg) in Et₂O (5 mL) was added a crystal of iodine followed by 0.3 mL of 2-(bromomethyl)-1-fluoro-4-(trifluoromethyl)benzene under argon. The reaction was initiated with a high intensity heat gun, then 2-(bromomethyl)-1-fluoro-4-(trifluoromethyl)benzene (2.5 g, 9.73 mmol) in Et₂O (5 mL) was added slowly (maintaining reflux). After addition was completed the reaction mixture was refluxed for 50 min, cooled to room temperature. A solution of 1-benzylpiperidin-4-one (1.84 g, 9.73 mmol) in Et₂O (10 mL) was added slowly with vigorous stirring. After addition was completed, the reaction mixture was left at room temperature for 50 min, saturated aqueous NH₄Cl solution was added and stirred at room temperature until hydrolysis was finished, extracted with ethyl acetate. The combined organic layer was washed with water, dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.2% NH₄OH) to give the subtitled compound (720 mg).

APCI-MS: m/z 368 (MH⁺).

(ii) 1'-Benzyl-5-(trifluoromethyl)-3H-spiro[1-benzofuran-2,4'-piperidine]

To a suspension of NaH (55%) (127 mg, 2.91 mmol) in toluene (4 mL) was slowly added a solution of 1-benzyl-4-[2-fluoro-5-(trifluoromethyl) benzyl] piperidin-4 (715 mg, 1.94 mmol) in toluene (5 mL) at room temperature. After addition was completed the reaction mixture was stirred at 110 °C for 5 min, then DMF (3 mL) was added and the reaction mixture was stirred at reflux temperature for 40 min, cooled to room temperature, H₂O (3 mL) was added, extracted with ethyl acetate. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.2% NH₄OH) to give the subtitled compound (380 mg).
¹H-NMR (CDCl₃, 400 MHz): δ 7.45-7.23 (m, 6H); 6.82 (d, *J* = 9.0 Hz, 1H); 3.60 (s, 2H); 3.02 (s, 2H); 2.70-2.45 (m, 4H); 2.00 (m, 2H); 1.85 (m, 2H).
APCI-MS: m/z 348 (MH⁺).

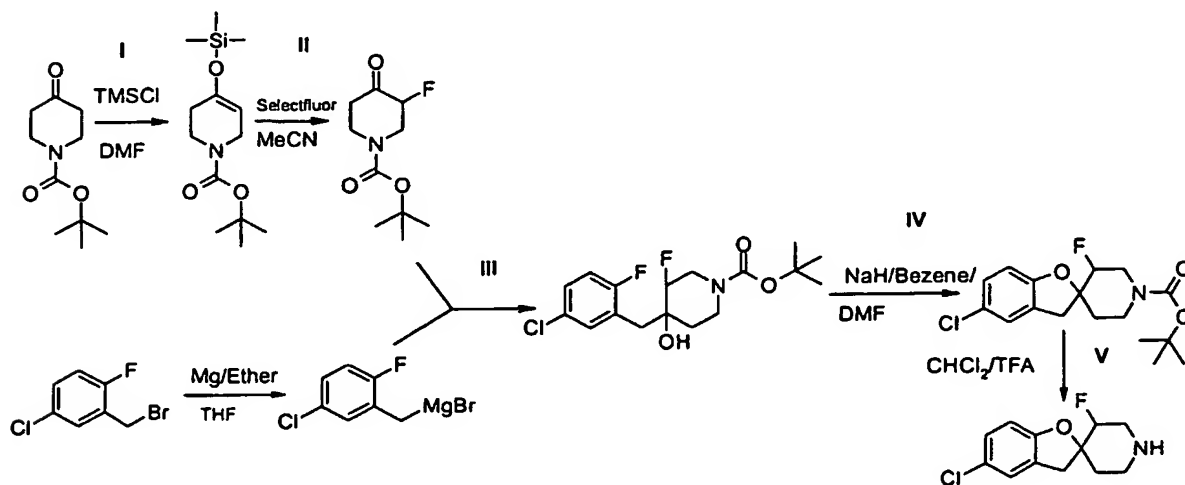
(iii) 5-(Trifluoromethyl)-3H-spiro[1-benzofuran-2,4'-piperidine]

To a solution of 1'-benzyl-5-(trifluoromethyl)-3H-spiro[1-benzofuran-2,4'-piperidin] (280 mg, 0.806 mmol) in toluene (3 mL) was added ethylchloroformate (0.093 mL, 0.967 mmol) and the reaction mixture was stirred at reflux temperature overnight, cooled to room temperature, diluted by addition of toluene and washed with aqueous NaHCO₃ and water successively. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was dissolved in ethanol ((4 mL), aqueous KOH (1.14 g KOH in 1.2 mL of H₂O) was added and the reaction mixture was refluxed overnight, cooled to room temperature, ethanol was removed in vacuo. Aqueous layer was extracted with Et₂O, combined ether layer was washed with 3N aqueous HCl. Combined acidic layer was made pH 10 by addition of aqueous NaOH. The basic solution was extracted with ethyl acetate. The combined organic layer was washed with water, dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH₄OH) to give the subtitled compound (156 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.29 (s, 1H); 7.39 (d, *J* = 8.4 Hz, 1H); 6.82 (d, *J* = 8.4 Hz, 1H); 3.10-3.00 (m, 4H); 2.89-2.81 (m, 2H); 1.94-1.86 (m, 2H); 1.82-1.74 (m, 2H).

APCI-MS: *m/z* 258 (MH⁺).

Intermediate compound: 5-chloro-3'-fluoro-3H-spiro[1-benzofuran-2,4'-piperidine]



(i) *tert*-Butyl 4-[(trimethylsilyl)oxy]-3,6-dihydropyridine-1(2*H*)-carboxylate

To a solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (10.13g, 50.84mmol) in DMF under argon was added TMSCl (7.74 ml, 61.27mmol) followed by Et₃N (17 ml). The mixture was stirred at 80°C overnight. The solution was cooled to ambient temperature and then diluted with heptane, washed with conc. aq NaHCO₃ and water. The organic layer
5 was then dried over sodium sulphate, filtered and concentrated. Chromatographic purification on silica gel (EtOAc:pethroleum ether 40-60 1:9) gave 9.6g (69 %) of an oil which solidified on standing.

¹H-NMR (CDCl₃, 300 MHz): δ 4.79(m, 1H); 3.87(m, 2H); 3.52(t, *J* = 5,8 Hz, 2H); 2.11(m, 2H); 1.47(s, 9H); 0.19(s, 9H).

10 APCI-MS: *m/z* 272 (M+H)⁺.

(ii) *tert*-Butyl 3-fluoro-4-oxopiperidine-1-carboxylate

To a solution of *tert*-Butyl 4-[(trimethylsilyl)oxy]-3,6-dihydropyridine-1(2*H*)-carboxylate (9.52 g, 35.07 mmol) in CH₃CN under argon was added selectfluor reagent (13.7 g, 38.6
15 mmol) and stirred at room temp. for 2 h. The reaction mixture was diluted with EtOAc (1000ml), washed with dilute brine, water, dried over sodium sulphate, filtered and concentrated in vacuo. Chromatographic purification on silica gel (MeOH:EtOAc, from 0:1 to 2:98) gave 5.35g (70%) of an oil, which solidified on standing.

¹H-NMR (CDCl₃, 300 MHz): δ 4.73 - 4.94 (m, 1H), 4.14 - 4.23 (m, 2H), 3.30 - 3.20 (m, 2H) 2.49 - 2.66 (m, 2H), 1.50 (s, 9H)

20 APCI-MS: *m/z* 218 (M+H)⁺

(iii) *tert*-Butyl 4-(5-chloro-2-fluorobenzyl)-3-fluoro-4-hydroxypiperidine-1-carboxylate

25 To magnesium turnings covered with ether was added a small amount of a solution of 2-(bromomethyl)-4-chloro-1-fluorobenzene in diethyl ether and the reaction was initiated by a high intensity heat gun. To the refluxing mixture was added the remaining solution (150ml) dropwise maintaining the reflux. After all the solution was added the mixture was stirred until the reflux was ceased. A solution of *tert*-butyl 3-fluoro-4-oxopiperidine-1-
30 carboxylate in diethylether (50ml) was added slowly. The resulting mixture was stirred for

further 4 s at room temp., then it was quenched by slow addition sat. aq ammonium chloride (125ml). It was extracted with EtOAc (2 x 150ml), washed with brine, water, dried over sodium sulphate, filtered and concentrated. The resulting residue was purified on silica gel (heptane - Et₂O 4:1-2:1) to give 1.61 g (18%) of subtitle compound.

¹H-NMR (CDCl₃, 300 MHz): δ 6.74 (s, 1H), 7.15 (s, 1H), 7.10 - 7.14 (m, 1H), 4.85 - 5.02 (m, 1H), 3.78 - 3.88 (m, 2H), 3.50 (m, 2H) 2.74 (s, 2H), 1.63 - 1.67 (m, 2H), 1.44 (s, 9H)
APCI-MS: m/z 362 (M+H)⁺

(iv) *tert*-Butyl 5-chloro-3'-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

To a suspension of NaH (60% in mineral oil, 1.38 g, 4.35 mmol) in benzene (30 ml) was added a solution of *tert*-butyl 4-(5-chloro-2-fluorobenzyl)-3-fluoro-4-hydroxypiperidine-1-carboxylate in benzene (50ml) and the mixture was heated to reflux. DMF 20(ml) was added and refluxing continued for 6hrs. The mixture was cooled to rt and poured into water and extracted with ETOAc. The organic layer was dried over sodium sulphate, filtered and concentrated. The residue was purified by chromatography on SiO₂ (ethylacetate: n-heptane) to give the product (10 mg, 26%).

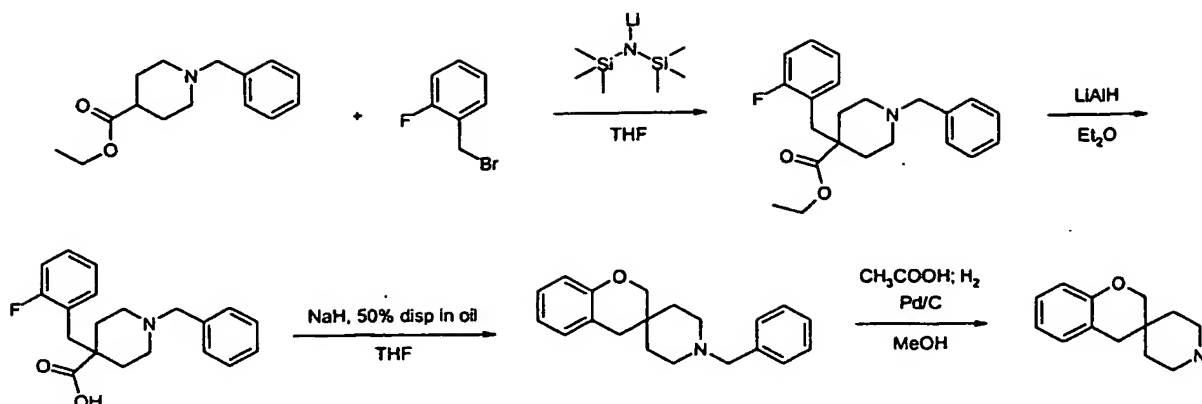
APCI-MS m/z 342 [M+H]⁺

(v) 5-Chloro-3'-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine]

A solution of *tert*-butyl 5-chloro-3'-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate in DCM/TFA (20ml, 5:2) was stirred at room temp. for 2 h. the solvent was removed in vacuo, the residue diluted with EtOAc and washed with sat. aq. NaHCO₃, and water. The organic layer was dried over Na₂SO₄, filtered and concentrated to give the title compound (60mg).

APCI-MS m/z 242 [M+H]⁺

Intermediate compound: 4*H*-spiro[chromene-3,4'-piperidine]



(i) Ethyl 1-benzyl-4-(2-fluorobenzyl)piperidine-4-carboxylate

Ethyl 1-benzylpiperidine-4-carboxylate (2.47 g, 10 mmol) was dissolved in tetrahydrofuran (20 mL) and cooled to -78°C. Lithium bis(trimethylsilyl) amide (11 mL, 1.0 M in tetrahydrofuran) was added slowly, and stirred for 30 minutes. 2-fluorobenzylbromide (1.34 mL, 11 mmol) in 5 mL tetrahydrofuran was added slowly. The resulting solution was allowed to reach room temperature and stirred over night. The reaction was quenched with ammonium chloride (aq, sat) and partitioned between water and ethyl acetate. The organic layer was washed with brine and dried over magnesium sulphate, filtrated and concentrated. The crude material was purified on silica (heptane/ethyl acetate), to give 2.7 g (77%) the subtitle compound as a colourless oil. APCI-MS: m/z 356 [MH⁺]

(ii) [1-Benzyl-4-(2-fluorobenzyl)piperidin-4-yl]methanol

A stirred solution of ethyl 1-benzyl-4-(2-fluorobenzyl)piperidine-4-carboxylate (1.85 g, 5.2 mmol) in diethyl ether was cooled on ice/sodium chloride. Lithium aluminium hydride (5.8 mL, 1.0 M in diethyl ether) was added drop wise. After stirring at room temperature for 2 hrs the mixture was re-cooled on ice, quenched with water/sodium hydroxide (10%) and stirred at room temperature for 1 hrs. The solids were filtered off, and the organic layer was dried over disodium sulphate, filtrated and concentrated. The crude material was purified on silica (dichloromethane/ethanol) to give 1.0 g (61%) the subtitle compound. APCI-MS: m/z 314 [MH⁺]

(iii) 1'-Benzyl-4H-spiro[chromene-3,4'-piperidine]

Sodium hydride (350 mg, 7.0 mmol, 50% disp in oil) was washed three times with heptane, under nitrogen atmosphere, and then dissolved in tetrahydrofuran (50 mL). A solution of [1-benzyl-4-(2-fluorobenzyl)piperidin-4-yl]methanol (1 g, 3.2 mmol) in tetrahydrofuran (30 mL) was added and the resulting mixture was refluxed for 3 hrs. The cooled solution was partitioned between water and ethyl acetate and the organic layer was dried over magnesium sulphate and concentrated. The crude product was purified on silica (dichloromethane/ methanol) to give 0.83 g (89%) of the subtitle compound.

APCI-MS: m/z 294 [MH⁺]

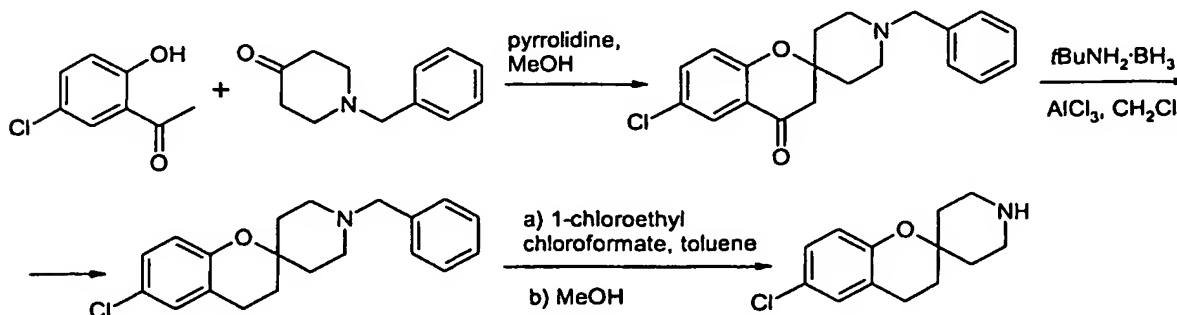
(iv) 4H-Spiro[chromene-3,4'-piperidine]

1'-benzyl-4H-spiro[chromene-3,4'-piperidine] (800 mg, 2.7 mmol) was dissolved in methanol (100 mL). Acetic acid (5 mL) and palladium on activated charcoal (cat amount, 10%) was added. Reaction in a Parr apparatus at 35 psi for 18 hrs, followed by filtration, evaporation and HPLC purification on C18 (acetonitrile/water) yielded 500 mg (92%) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆) δ: 8.86 (1H, bs); 7.10-7.05 (2H, m); 6.85 (1H, dt); 6.76 (1H, d); 3.93 (2H, s); 3.15-3.01 (4H, m); 2.71 (2H, s); 1.66-1.51 (4H, m)

APCI-MS: m/z 204 [MH⁺]

Intermediate compound: 6-Chloro-3,4-dihydrospiro[chromene-2,4'-piperidine]



(i) 1'-Benzyl-6-chlorospiro[chromene-2,4'-piperidin]-4(3H)-one

A solution of 1-(5-chloro-2-hydroxyphenyl)ethanone (1.7 g, 10 mmol), 1-benzylpiperidin-4-one (2.08 g, 11 mmol) and pyrrolidine (1.07 g, 15 mmol) in methanol (2 ml) was heated

at 70 °C for 3 h. After cooling to room temperature, the reaction mixture was poured into water (20 ml), and extracted with ethyl acetate (50 ml). The organic layer was washed with 1 N aq. HCl (2 x 50 ml), 2 N aq. NaOH (50 ml), and water. Drying over Na₂SO₄ and evaporation of solvent afforded subtitle compound as orange-coloured oil (2.61 g, 77 %).

5 APCI-MS: m/z 342 [M+H]⁺

(ii) 1'-Benzyl-6-chloro-3,4-dihydrospiro[chromene-2,4'-piperidine]

To a stirred suspension of AlCl₃ (3.04 g, 22.8 mmol) in dichloromethane (75 ml) *tert*-butylamine - borane (1:1) (3.98 g, 45.8 mmol) was added at 0 °C, and the stirring was
10 continued for 15 min at this temperature to obtain a clear solution. A solution of 1'-benzyl-6-chlorospiro[chromene-2,4'-piperidin]-4(3*H*)-one (2.61 g, 7.6 mmol) in dichloromethane (15 ml) was added dropwise. The stirring was continued for 2 h at 0 °C and for 3 h at room temperature. The reaction mixture was quenched by dropwise addition of 0.1 N aq. HCl. After the gas evolution has ceased, the layers were separated. The organic layer was
15 washed with 0.1 N HCl (2 x 50 ml) and brine (50 ml), and dried over Na₂SO₄. The solvent was removed in vacuo to afford subtitle compound as colourless solid (1.63 g, 65 %).

APCI-MS: m/z 328 [M+H]⁺

(iii) 6-Chloro-3,4-dihydrospiro[chromene-2,4'-piperidine] hydrochloride

20 A solution of 1'-benzyl-6-chloro-3,4-dihydrospiro[chromene-2,4'-piperidine] (1.63 g, 5.0 mmol) and 1-chloroethyl chloroformate (1.07 g, 7.5 mmol) in toluene (5 ml) was heated with reflux overnight. The solvent was removed i. vacuo, the oily residue dissolved in methanol (10 ml) and heated with reflux overnight. The solvent was removed in vacuo, and the residue treated with diethyl ether (50 ml). The white precipitate was collected by
25 filtration, washed with diethyl ether and dried to afford the subtitle compound as white powder (0.58 g, 49 %).

¹H-NMR (CDCl₃, 400 MHz): δ 7.07 (d, *J* = 10.0 Hz, 2H); 7.63 (d, *J* = 8.4 Hz, 1H); 3.2 – 3.5 (m, 4H); 2.77 (t, *J* = 6.6 Hz, 2H); 1.9 – 2.2 (m, 4H); 1.88 (t, *J* = 6.6 Hz, 2H).

APCI-MS: m/z 238 [M+H]⁺

Intermediate compound: 6-Chloro-3H-spiro[2-benzofuran-1,4'-piperidine]**(i) 1'-Benzyl-6-chloro-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one**

To a solution of 2-bromo-4-chlorobenzoic acid (2.35 g, 10.0 mmol) in tetrahydrofuran (THF) (15 mL) was added, a 1.6 M solution in hexane, n-butyllithium (Parham, W.E; Egberg, D. C; Sayed, Y. A; Thraikill, R. W; Keyser, G. E; William, M. N; Montgomery, M. C; Jones, L. D., *J. Org. Chem.*, 1976, 41, 2628-2633) (20 mL, 32.0 mmol) slowly at -78 °C under nitrogen. After addition was complete the reaction mixture was stirred at -78 °C for 3 hours (h). Then a solution of 1-benzylpiperidin-4-one (3.78 g, 20.0 mmol) in THF (10 mL) was added slowly to the reaction mixture at -78 °C. After addition was complete the reaction temperature was raised to room temperature and the reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into a mixture of water (H₂O) (60 mL) and diethyl ether (60 mL), layers were separated. The aqueous layer was extracted with diethyl ether (2 x 20 mL). The aqueous layer was acidified with aq 6 M HCl to pH 2 and boiled for 1 h, cooled to 0 °C, pH was adjusted to 10 by addition of aqueous sodium hydroxide (NaOH) (6M) and rapidly extracted with trichloromethane (CHCl₃). The organic layer was washed with H₂O, dried over sodium sulphate (Na₂SO₄), filtered and concentrated in vacuo to give sub-titled compound (1.22 g) and it was pure enough for the next step.

¹H-NMR (CDCl₃, 400 MHz): δ 7.84 (d, *J* = 8.2 Hz, 1H); 7.51 (dd, *J* = 1.7, 8.2 Hz, 1H); 7.45-7.25 (m, 6H); 3.67 (s, 2H); 3.00 (br.d; *J* = 9.4 Hz, 2H); 2.61 (br.t, *J* = 11.2 Hz, 2H); 2.32 (br, s, 2H); 1.74 (d, *J* = 12.2 Hz, 2H).

APCI-MS: *m/z* 328(MH⁺).

(ii) 1'-Benzyl-6-chloro-3H-spiro[2-benzofuran-1,4'-piperidine]

To a solution of 1'-benzyl-6-chloro-3H-spiro[2-benzofuran-1,4'-piperidine]-3-one (1.1 g, 3.35 mmol) in THF (15 mL) was added 1 M solution of borane (Marxer, A; Rodriguez, H. R; McKenna, J. M; Tsai, H. M., *J. Org. Chem.*, 1975, 40, 1427-1430) complex in THF (7 mL, 7.0 mmol) slowly at 0 °C. After addition was complete, the reaction mixture was kept at room temperature for 30 minutes (min), then kept at reflux overnight, cooled to

0 °C and 6M aqueous hydrochloric acid (HCl) (3.5 mL) was added slowly. The reaction mixture was kept at reflux for 5 h, cooled to 0 °C, pH of the reaction mixture was adjusted to 10 by addition of aqueous NaOH 6M and the whole was extracted with ethyl acetate. The organic layer was washed with H₂O, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel flash chromatography (0-30% ethyl acetate in petroleum ether) to give the sub-titled compound (900 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 7.44-7.22 (m, 6H); 7.18 (m, 2H); 5.03 (s, 2H); 3.60 (s, 2H); 2.87 (br.d, *J* = 10.5 Hz, 2H); 2.45 (br.t, *J* = 11.2 Hz, 2H); 2.00 (br.s, 2H); 1.79 (d, *J* = 11.2 Hz, 2H).

APCI-MS: *m/z* 314(MH⁺).

(iii) 6-Chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine]

To a solution of 1'-benzyl-6-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (850 mg, 2.7 mmol) in dichloromethane (CH₂Cl₂) (8 mL) was added chloroethyl chloroformate (Yang, B. V; o'Rourke, D; Li, J., *Synlett*, 1993, 195-196) (772 mg, 5.4 mmol) slowly at 0 °C. After addition was complete the reaction mixture was stirred at 0 °C for 30 min. The volatiles were removed in vacuo, residue was dissolved in methanol (10 mL) and kept at reflux for 40 min. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-6% methanol in dichloromethane, 0.2% ammonium hydroxide (NH₄OH)) to give the titled compound (170 mg) and 1'-benzyl-6-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine] was recovered (200 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.29-7.21 (m, 3H); 5.00 (s, 2H); 2.99 (m, 4H); 1.90-1.81 (m, 2H); 1.70 (m, 2H).

APCI-MS: *m/z* 224(MH⁺).

Intermediate compound: 5-Fluoro-3*H*-spiro[2-benzofuran-1,4'-piperidine]**(iv) 1'-Benzyl-5-fluoro-3*H*-spiro[2-benzofuran-1,4'-piperidin]-3-one**

This reaction was performed as described for (i) above using 2-bromo-5-fluorobenzoic acid (2.19 g, 10.0 mmol), 1-benzylpiperidin-4-one (3.78 g, 20.0 mmol), n-butyl lithium (n-BuLi) (20 mL) and THF (20 mL) to give the sub-titled compound.

¹H-NMR (CDCl₃, 400 MHz): δ 7.58-7.23 (m, 8H); 3.68 (s, 2H); 2.98 (m, 2H); 2.59 (m, 2H); 2.28 (m, 2H); 1.74 (m, 2H).

APCI-MS: m/z 312(MH⁺).

(v) 1'-Benzyl-5-fluoro-3*H*-spiro[2-benzofuran-1,4'-piperidine]

This reaction was performed as described for (ii) above using 1'-benzyl-5-fluoro-3*H*-spiro[2-benzofuran-1,4'-piperidin]-3-one (200 mg, 0.642 mmol), borane THF complex 1M solution (1.34 mL, 1.34 mmol) and THF (3 mL) to give the sub-titled compound (148 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 7.41-7.27 (m, 5H); 7.08 (dd, *J* = 4.8, 8.3 Hz, 1H); 6.97 (m, 1H); 6.89 (m, 1H); 5.08 (s, 2H); 3.60 (s, 2H); 2.87 (m, 2H); 2.46 (m, 2H); 1.97 (m, 2H); 1.88 (m, 2H).

APCI-MS: m/z 298(MH⁺).

(vi) 5-Fluoro-3*H*-spiro[2-benzofuran-1,4'-piperidine]

This reaction was performed as described for (iii) above using 1'-benzyl-5-fluoro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (145 mg, 0.487 mmol), chloroethyl chloroformate (0.07 mL) to give the titled compound.

¹H-NMR (CD₃OD, 400 MHz): δ 7.18 (dd, *J* = 4.9, 8.1 Hz, 1H); 7.03-6.96 (m, 2H); 5.01 (s, 2H); 3.09-2.93 (m, 4H); 1.91-1.81 (m, 2H); 1.73-1.66 (m, 2H).

APCI-MS: m/z 208(MH⁺).

Intermediate compound: [(2*S*)-2-methyloxiran-2-yl]methyl 3-nitrobenzenesulfonate

Prepared as described by Eriksson, T.; Klingstedt, T.; Mussie, T., Published International Patent Application No. WO 01/98273.

Example 1***N*-(2-([(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide**

5

Step I:***N*-(2-[(2*S*)-Oxiran-2-ylmethoxy]phenyl)acetamide**

A mixture of *N*-(2-hydroxyphenyl)acetamide (1.51 g, 10 mmol), (2*S*)-oxiran-2-ylmethyl-3-nitrobenzenesulfonate (2.59 g, 10 mmol) and cesium carbonate (Cs₂CO₃) (3.9 g, 12 mmol) in dimethylformamide (DMF) (30 mL) was stirred at room temperature overnight. The
10 reaction mixture was partitioned between ethyl acetate and H₂O. The organic layer was dried over Na₂SO₄, filtered, concentrated and the residue was purified by silica gel flash chromatography to give the subtitled compound (1.34 g).

¹H-NMR (CDCl₃, 400 MHz): δ 8.40 (m, 1H); 7.90 (br.,s, 1H); 7.05 (m, 2H); 6.92 (m, 1H);
15 4.37 (dd, *J* = 2.5, 11.3 Hz, 1H); 3.98 (dd, *J* = 5.9, 11.3 Hz, 1H); 3.40 (m, 1H); 2.97 (t, *J* = 4.8 Hz, 1H); 2.81 (dd, *J* = 2.7, 4.8 Hz, 1H); 2.20 (s, 3H).

Step II:***N*-(2-([(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide**
20

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (36 mg, 0.16 mmol) and *N*-(2-[(2*S*)-oxiran-2-ylmethoxy]phenyl)acetamide (33 mg, 0.16 mmol) in ethanol (3 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane containing
25 0.2% ammonium hydroxide) to give the titled compound (25 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 7.82 (d, *J* = 4.8 Hz, 1H); 7.22 (m, 1H); 7.13 (m, 2H); 7.05 (d, *J* = 7.5 Hz, 1H); 6.98 (m, 1H); 6.74 (d, *J* = 8.6 Hz, 1H); 4.49 (m, 1H); 4.08 (d, *J* = 4.8 Hz, 2H); 3.70 (m, 2H); 3.43 (m, 4H); 3.12 (s, 2H); 2.20 (m, 7H).

APCI-MS: *m/z* 433 (MH⁺).

Example 2

***N*-(2-{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorophenyl)acetamide**

5 Step I:

***N*-(4-Fluoro-2-hydroxyphenyl)acetamide**

A mixture of 5-fluoro-2-nitrophenol (5 g, 31.8 mmol), acetic anhydride (4.86 g, 47.7 mmol) and platinum on carbon (5%, 200 mg) in methanol was hydrogenated at 35 psi for 3 hours. The catalyst was filtered off and the residue was purified by silica gel flash
10 chromatography to give the subtitled compound (4.7 g).

¹H-NMR (CD₃OD, 300 MHz): δ 7.56-7.51 (m, 1H); 6.61-6.50 (m, 2H); 2.15 (s, 3H).

APCI-MS: m/z 170 (MH⁺).

Step II:

15 ***N*-(4-Fluoro-2-[(2*S*)-oxiran-2-ylmethoxy]phenyl)acetamide**

A mixture of *N*-(4-fluoro-2-hydroxyphenyl)acetamide (1.69 g, 10.0 mmol), (2*S*)-oxiran-2-ylmethyl-3-nitrobenzenesulfonate (2.59 g, 10.0 mmol) and Cs₂CO₃ (4.87 g, 15.0 mmol) in DMF (15 mL) was stirred at room temperature for 2 h. The reaction mixture was partitioned between ethylacetate and H₂O. The organic layer was dried over Na₂SO₄
20 filtered and concentrated. The residue was purified by silica gel flash chromatography to give the subtitled compound (1.35 g).

¹H-NMR (CDCl₃, 400 MHz): δ 8.33-8.29 (m, 1H); 7.71 (br. s, 1H), 6.74-6.66 (m, 2H); 4.39-4.36 (m, 1H); 3.95-3.90 (m, 1H); 3.41-3.39 (m, 1H); 2.99-2.97 (m, 1H); 2.80-2.79 (m, 1H).

25 APCI-MS: m/z 226 (MH⁺).

Step III:***N*-(2-{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorophenyl)acetamide**

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (45 mg, 0.201 mmol) and
5 *N*-{4-fluoro-2-[(2*S*)-oxiran-2-ylmethoxy]phenyl}acetamide (45.3 mg, 0.201 mmol) in ethanol (3 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (33 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 8.52 (s, 1H); 8.20 (dd, *J* = 6.4, 8.9 Hz, 1H); 7.18 (s, 1H);
10 7.13 (dd, *J* = 2.0, 8.5 Hz, 1H); 6.74 (dd, *J* = 2.6, 8.6 Hz, 1H); 6.69 (d, *J* = 8.6 Hz, 1H); 6.59 (dd, *J* = 2.6, 9.8 Hz, 1H); 4.48 (m, 1H); 4.17 (dd, *J* = 3.7, 9.8 Hz, 1H); 4.00 (dd, *J* = 2.2, 9.8 Hz, 1H); 3.79 (m, 2H); 3.59 (br.d, *J* = 11.7 Hz, 1H); 3.38 (m, 1H); 3.27 (m, 1H); 3.12 (s, 2H); 3.05 (m, 1H); 2.48 (m, 1H); 2.37 (m, 1H); 2.24 (s, 3H); 2.17 (m, 2H).

APCI-MS: *m/z* 451 (MH⁺).

Example 3***N*-(2-{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-methoxyphenyl)acetamide****Step I:*****N*-(2-Hydroxy-4 methoxyphenyl)acetamide**

2-Nitro-5-methoxyphenol (prepared from 3-methoxyphenol, R. J. Maleski, *Synthetic Communications*, 1993, 23, 343-348) (48.5g, 0.287 mol) dissolved in THF (1.5 L) was hydrogenated at ambient temperature over night with 10% palladium on carbon (10 g) until
20 20.3 L of hydrogen was consumed. After filtration and evaporation the residue was suspended in degassed water (1.7 L) and acetic anhydride (42.5 mL) was added with stirring. The mixture was heated to 60 °C for 1h and then cooled to room temperature. The volatiles were removed in vacuo and the solid was washed thoroughly with water and dried in vacuo to give brick-red crystals (41.7 g, 80 %).

¹H-NMR (400 MHz, CDCl₃): δ 8.98 (s, 1H); 7.34 (br.s, 1H); 6.81 (d, 1H); 6.58 (d, 1H); 6.44 (dd, 1H); 3.78 (s, 3H); 2.26 (s, 3H)

Step II:

5 ***N*-{4-Methoxy-2[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide**

N-(2-Hydroxy-4-methoxyphenyl)acetamide (18.12 g, 0.1 mol) and (2S)-oxiran-2-ylmethyl-3-nitrobenzenesulfonate (25.92 g, 0.1 mol) were dissolved in dry DMF (75 mL) and stirred under nitrogen (N₂) on an ice-bath. Cesium carbonate (35.8g, 0.11 mol) was added and the stirring under N₂ was continued at ambient temperature overnight. The mixture was
10 poured into ethyl acetate (1L) and water (250 mL). The organic phase was washed with water (3 x 250 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to give an orange solid crude product (29 g), which was recrystallized from ethanol (100 mL) and washed with ether to give white crystals. More white crystals were obtained from the mother liquor, after evaporation and recrystallization from 2-propanol. Total yield 15 g
15 (63%).

¹H-NMR (CDCl₃): δ 8.22 (d, 1H); 7.64 (bs, 1H); 6.53 (dd, 1H); 6.50 (d, 1H); 4.34 (dd, 1H); 3.92 (dd, 1H); 3.79 (s, 3H); 3.38 (m, 1H); 2.96 (t, 1H); 2.78 (dd, 1H); 2.20 (s, 3H)

Step III:

20 ***N*-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-methoxyphenyl)acetamide**

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (200 mg, 0.894 mmol) and *N*-{4-methoxy-2[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide (212 mg, 0.894 mmol) in ethanol (5 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and
25 the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (400 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.74 (d, *J* = 8.9 Hz, 1H); 7.13 (m, 1H); 7.04 (dd, *J* = 2.3, 8.5 Hz, 1H); 6.65 (d, *J* = 8.5 Hz, 1H); 6.61 (d, *J* = 2.7 Hz, 1H); 6.51 (dd, *J* = 2.7, 8.8 Hz, 1H); 4.17 (m, 1H); 4.08 (dd, *J* = 3.4, 10.0 Hz, 1H); 3.98 (dd, *J* = 6.3, 9.9 Hz, 1H); 3.79 (s,
30 3H); 3.03 (s, 2H); 2.72 (m, 4H); 2.62 (m, 2H); 2.15 (s, 3H); 1.95 (m, 2H); 1.84 (m, 2H).

APCI-MS: m/z 461 (MH^+).

Example 4

***N*-(2-(((2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-hydroxyphenyl)acetamide**

To a cold (0 °C) solution of *N*-(2-(((2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-methoxyphenyl)acetamide (380 mg, 0.82 mmol) in dichloromethane (8 mL) was added 1M solution of boron tribromide (BBr_3) in dichloromethane (2.47 mL, 2.47 mmol) slowly. After addition was complete the icebath was removed and the reaction mixture was stirred at room temperature for 2 h 30 min. The reaction mixture was cooled to 0 °C and methanol (2 mL) was added slowly with stirring for 10 min. The volatiles were removed in vacuo. The residue was dissolved in large volume of ethyl acetate, washed successively with aqueous sodium hydrogencarbonate (NaHCO₃) solution and water. The organic layer was dried over Na₂SO₄, filtered, concentrated and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (155 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.57 (d, J = 8.7 Hz, 1H); 7.14 (m, 1H); 7.04 (dd, J = 2.3, 8.5 Hz, 1H); 6.66 (d, J = 8.5 Hz, 1H); 6.48 (d, J = 2.5 Hz, 1H); 6.32 (dd, J = 2.5, 8.6 Hz, 1H); 4.17 (m, 1H); 4.06 (dd, J = 3.4, 9.8 Hz, 1H); 3.93 (dd, J = 6.2, 9.8 Hz, 1H); 3.03 (s, 2H); 2.70 (m, 4H); 2.59 (m, 2H); 2.13 (s, 3H); 1.95 (m, 2H); 1.84 (m, 2H).

APCI-MS: m/z 447 (MH^+).

Example 5

***N*-[2-(((2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-5-(trifluoromethyl)phenyl]acetamide**

Step I:

***N*-[2-(((2*S*)-2-Methyloxiran-2-yl]methoxy)-5-(trifluoromethyl)phenyl] acetamide**

A mixture of 2-nitro-4-(trifluoromethyl)phenol (310 mg, 1.5 mmol), palladium on carbon (10%, 125 mg) and acetic anhydride (306.3 mg, 3.0 mmol) in methanol was hydrogenated for 2 h at atmospheric pressure. The catalyst was filtered off, the filtrate was concentrated in vacuo to give crude *N*-[2-hydroxy-5-(trifluoromethyl)phenyl]acetamide (331 mg). A part (219.16 mg, 1.0 mmol) of *N*-[2-hydroxy-5-(trifluoromethyl)phenyl]acetamide was treated with [(2*S*)-2-methyloxiran-2-yl]methyl 3-nitrobenzenesulfonate (273.27 mg, 1.0 mmol) in the presence of Cs₂CO₃ (406.25 mg, 1.25 mmol) in DMF (5 mL) at room temperature for 5 h. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na₂SO₄, filtered, concentrated. The residue was purified by silica gel flash chromatography (0-40% ethyl acetate in petroleum ether) to give the subtitled compound (230 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 8.86 (s, 1H); 8.00 (br.s, 1H); 7.29 (m, 1H); 6.97 (d, *J* = 8.5 Hz, 1H); 4.23 (d, *J* = 11.0 Hz, 1H); 4.04 (d, *J* = 11.03 Hz, 1H); 2.93 (m, 1H); 2.81 (d, *J* = 4.6 Hz, 1H); 2.22 (s, 3H); 1.42 (s, 3H).

Step II:

N-[2-{{{(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-5-(trifluoromethyl)phenyl]acetamide

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (35 mg, 0.155 mmol) and *N*-[2-{{{(2*S*)-2-methyloxiran-2-yl}methoxy}-5-(trifluoromethyl)phenyl] acetamide (45 mg, 0.155 mmol) in ethanol (2 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (28 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 8.40 (d, *J* = 1.8 Hz, 1H); 7.40 (dd, *J* = 1.4, 8.7 Hz, 1H); 7.18 (d, *J* = 8.6 Hz, 1H); 7.13 (m, 1H); 7.03 (dd, *J* = 2.2, 8.5 Hz, 1H); 6.63 (d, *J* = 8.5 Hz, 1H); 4.13 (d, *J* = 9.3 Hz, 1H); 3.98 (d, *J* = 9.3 Hz, 1H); 2.99 (s, 2H); 2.78 (m, 1H); 2.68 (m, 3H); 2.58 (m, 1H); 2.22 (s, 3H); 1.88 (m, 2H); 1.78 (m, 2H); 1.32 (s, 3H).

APCI-MS: *m/z* 513 (MH⁺).

Example 6

2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-*N*-cyclopropylbenzamide

Step I:

5 *N*-Cyclopropyl-2-hydroxybenzamide

A mixture of methyl salicylate (4.36 g, 28.69 mmol) and cyclopropylamine (1.64 g) was heated in a sealed tube at 80-100 °C for 3h. An additional 0.5 g of cyclopropylamine was added and heated at 70 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography to give the subtitled compound (2.71 g).

10 ¹H-NMR (CDCl₃, 400 MHz): δ 12.40 (s, 1H); 7.40 (m, 1H); 7.38 (m, 1H); 7.01 (m, 1H); 6.81 (m, 1H); 6.48 (br.s, 1H); 2.85 (m, 1H); 0.98 (m, 2H); 0.82 (m, 2H).

Step II:

***N*-Cyclopropyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide**

15 A mixture of *N*-cyclopropyl-2-hydroxybenzamide (270 mg, 1.52 mmol), (2S)-oxiran-2-ylmethyl-3-nitrobenzenesulfonate (378 mg, 1.68 mmol) and cesium carbonate (645 mg, 1.98 mmol) in DMF (4 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash

20 chromatography (40% heptane in ethyl acetate) to give the subtitled compound (354 mg).
¹H-NMR (CDCl₃, 400 MHz): δ 8.22 (dd, *J* = 1.8, 7.8 Hz, 1H); 7.95 (br.s, 1H); 7.42 (m, 1H); 7.10 (m, 1H); 6.93 (d, *J* = 8.3 Hz, 1H); 4.44 (dd, *J* = 2.5, 10.7 Hz, 1H); 4.08 (dd, *J* = 5.1, 10.8 Hz, 1H); 3.40 (m, 1H); 3.04-2.95 (m, 2H); 2.83 (dd, *J* = 2.7, 4.5 Hz, 1H); 0.86 (m, 2H); 0.65 (m, 2H).

Step III:

2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-*N*-cyclopropylbenzamide

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (9 mg, 0.04 mmol) and
30 *N*-cyclopropyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide (9.4 mg, 0.4 mmol) in ethanol (1.5

mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (7 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.92 (m, 1H); 7.47 (m, 1H); 7.13 (m, 2H); 7.05 (m, 2H);
5 6.65 (d, *J* = 8.5 Hz, 1H); 4.23 (dd, *J* = 3.0, 9.4 Hz, 1H); 4.16 (m, 1H); 4.09 (dd, *J* = 5.5, 9.4 Hz, 1H); 3.03 (s, 2H); 2.93 (m, 1H); 2.70 (br. S, 4H); 2.60 (d, *J* = 6.3 Hz, 1H); 1.96 (m, 2H); 1.85 (m, 2H); 0.81 (m, 2H); 0.69 (m, 2H).

APCI-MS: *m/z* 457 (MH⁺).

10 Example 7

2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-*N*-cyclopropyl-4-fluorobenzamide

Step I:

15 ***N*-Cyclopropyl-4-fluoro-2-hydroxybenzamide**

A suspension of methyl 4-fluoro-2-hydroxybenzoate (510 mg, 3.0 mmol) in cyclopropylamine (5 mL) was stirred at room temperature overnight when it became a clear solution. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-30% ethyl acetate in petroleum ether) to give the subtitled
20 compound (493 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 12.65 (s, 1H); 7.28 (m, 1H); 6.69 (dd, *J* = 2.6, 10.4 Hz, 1H); 6.56 (ddd, *J* = 2.6, 8.0, 10.4 Hz, 1H); 6.30 (br. S, 1H); 2.88 (m, 1H); 0.98 (m, 2H); 0.66 (m, 2H).

APCI-MS: *m/z* 196 (MH⁺).

25 **Step II:**

***N*-Cyclopropyl-4-fluoro-2-(oxiran-2-ylmethoxy)benzamide**

A mixture of *N*-cyclopropyl-4-fluoro-2-hydroxybenzamide (195 mg, 1.0 mmol), (2S)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (259 mg, 1.0 mmol) and Cs₂CO₃ (390 mg, 1.2
30 mmol) in DMF (5 mL) was stirred at room temperature overnight. The reaction mixture

was partitioned between ethyl acetate and water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-30% ethylacetate in petroleum ether) to give the subtitled compound (150 mg).

5 ¹H-NMR (CDCl₃, 400 MHz): δ 8.24 (dd, *J* = 7.0, 8.8 Hz, 1H); 7.80 (br. s, 1H); 6.82 (ddd, *J* = 2.3, 7.6, 10.2 Hz, 1H); 6.66 (dd, *J* = 2.3, 10.2 Hz, 1H); 4.45 (dd, *J* = 2.4, 10.7 Hz, 1H); 4.05 (dd, *J* = 5.1, 10.7 Hz, 1H); 3.40 (m, 1H); 3.00 (m, 2H); 2.84 (dd, *J* = 2.6, 4.8 Hz, 1H); 0.86 (m, 2H); 0.65 (m, 2H).
APCI-MS: *m/z* 252 (MH⁺).

10

Step III:

2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-N-cyclopropyl-4-fluorobenzamide

15 A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (30 mg, 0.134 mmol) and *N*-cyclopropyl-4-fluoro-2-(oxiran-2-ylmethoxy)benzamide (33.6 mg, 0.134 mmol) in ethanol (2 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (36 mg).

20 ¹H-NMR (CD₃OD, 400 MHz): δ 7.97 (dd, *J* = 6.9, 8.7 Hz, 1H); 7.14 (m, 1H); 7.05 (dd, *J* = 2.3, 8.5 Hz, 1H); 6.96 (dd, *J* = 2.4, 10.4 Hz, 1H); 6.82 (ddd, *J* = 2.4, 8.0, 10.4 Hz, 1H); 6.66 (d, *J* = 8.5 Hz, 1H); 4.24 (dd, *J* = 3.0, 9.4 Hz, 1H); 4.17 (m, 1H); 4.10 (dd, *J* = 5.5, 9.4 Hz, 1H); 3.05 (s, 2H); 2.82 (m, 1H); 2.71 (br. s, 4H); 2.60 (d, *J* = 6.3 Hz, 2H); 1.99 (m, 2H); 1.88 (m, 2H); 0.83 (m, 2H); 0.58 (m, 2H).

APCI-MS: *m/z* 252 (MH⁺).

25

Example 8

2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-N-cyclopropyl-4-methoxybenzamide

30 Step I:

***N*-Cyclopropyl-2-hydroxy-4-methoxybenzamide**

A suspension of methyl 2-hydroxy-4-methoxybenzoate (5.1 g, 28.0 mmol) in cyclopropyl amine (24 mL) was stirred at room temperature for 5 days. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-60% ethyl acetate in petroleum ether) to give the subtitled compound (1.8 g).

¹H-NMR (CD₃OD, 400 MHz): δ 7.61 (d, *J* = 8.8 Hz, 1H); 6.42 (m, 2H); 3.80 (s, 3H); 2.80 (m, 1H); 0.80 (m, 2H); 0.62 (m, 2H).

APCI-MS: *m/z* 208 (MH⁺)

Step II:***N*-Cyclopropyl-4-methoxy-2-[(2*S*)-oxiran-2-ylmethoxy]benzamide**

A mixture of *N*-cyclopropyl-2-hydroxy-4-methoxybenzamide (700 mg, 3.38 mmol), (2*S*)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (876 mg, 3.38 mmol) and Cs₂CO₃ (1.31 g, 4.05 mmol) in DMF (12 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-80% ethyl acetate in petroleum ether) to give the subtitled compound (1.0 g).

¹H-NMR (CDCl₃, 400 MHz): δ 8.20 (d, *J* = 8.8 Hz, 1H); 7.85 (br.s, 1H); 6.63 (dd, *J* = 2.3, 8.8 Hz, 1H); 6.45 (d, *J* = 2.3 Hz, 1H); 4.42 (dd, *J* = 2.5, 10.8 Hz, 1H); 4.05 (dd, *J* = 5.2, 10.8 Hz, 1H); 3.82 (s, 3H); 3.40 (m, 1H); 3.00 (m, 2H); 2.83 (dd, *J* = 2.6, 4.8 Hz, 1H); 0.88 (m, 2H); 0.68 (m, 2H).

APCI-MS: *m/z* 264 (MH⁺).

Step III:**2-[[[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-*N*-cyclopropyl-4-methoxybenzamide**

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (100 mg, 0.447 mmol) and *N*-cyclopropyl-4-methoxy-2-[(2*S*)-oxiran-2-ylmethoxy]benzamide (117.7 mg, 0.447 mmol) in ethanol (3 mL) was stirred at 80 °C overnight. The volatiles were removed in

vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (145 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 8.18 (m, 2H); 7.12 (m, 1H); 7.09 (dd, *J* = 2.3, 8.5 Hz, 1H); 6.70 (d, *J* = 8.5 Hz, 1H); 6.63 (dd, *J* = 2.3, 8.8 Hz, 1H); 6.44 (d, *J* = 2.3 Hz, 1H); 4.19 (dd, *J* = 3.3, 9.4 Hz, 1H); 4.13 (m, 1H); 3.97 (dd, *J* = 5.0, 9.4 Hz, 1H); 3.88 (s, 3H); 3.02 (m, 3H); 2.92 (m, 1H); 2.81 (m, 1H); 2.63 (m, 3H); 2.53 (dd, *J* = 3.6, 12.4 Hz, 1H); 2.04 (m, 2H); 1.88 (m, 2H); 0.85 (m, 2H); 0.06 (m, 2H).

APCI-MS: *m/z* 487 (MH⁺).

Example 9

N-(2-(((2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy)-4-hydroxyphenyl)acetamide trifluoroacetate

Step I:

2-Methyl-1,3-benzoxazol-6-ol

To a stirred solution of 1-(2,4-dihydroxyphenyl)ethanone (20 g, 131 mmol) in pyridine (80 mL) hydroxylamine hydrochloride (9.1 g, 131 mmol) was added over a period of 15 min in small portions at room temperature. The reaction mixture was stirred for 20 h and then diluted with water (600 mL) and extracted with ethyl acetate (2 x 250 mL). The combined organic extracts were washed with water (2 x 250 mL) and 5 % aqueous HCl (250 mL). The solvent was removed in vacuo. Water (200 mL) was added to the residue and then concentrated in vacuo, then toluene (200 mL) was added and concentrated in vacuo. The residue was dissolved in a mixture of acetonitrile (150 mL) and dimethylacetamide (25 mL). The solution was cooled to 5 °C, phosphorus oxychloride (20.4 g, 12.2 mL, 133 mmol) was added dropwise allowing the temperature to exceed 10 °C. After the addition was complete, the reaction mixture was stirred at room temperature for 1 h and then it was slowly poured into a mixture of sodium carbonate (55 g) and ice (ca 800 g). After the ice melted, the resulting slurry was filtered and the solid collected was washed with water (2 x 150 mL). The product was dried in vacuo to afford a yellow powder (14.4 g, 97 mmol, 76%).

¹H-NMR (400 MHz, DMSO-d₆): δ 9.68 (br. s, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 6.94 (d, *J* = 2.2 Hz, 1H), 6.74 (dd, *J* = 8.5, 2.2 Hz, 1H), 2.50 (s, 3H).

Step II:

2-Methyl-1,3-benzoxazol-6-yl benzoate

To a stirred suspension of 2-methyl-1,3-benzoxazol-6-ol (2.99 g, 20 mmol) in dichloromethane (50 mL) was added triethylamine (4.05 g, 5.58 mL, 40 mmol). A solution of benzoyl chloride (3.09 g, 2.56 mL, 22 mmol) in dichloromethane (20 mL) was added dropwise over ca. 10 min. The reaction mixture was stirred at room temperature for 2.5 h, then washed with water (2 x 50 mL), and dried over Na₂SO₄, filtered and concentrated in vacuo to give the subtitled compound as a colourless solid (5.05 g, 20 mmol).

¹H-NMR (400 MHz, CDCl₃): δ 8.22 (m, 2H), 7.66 (m, 2H), 7.53 (m, 2H), 7.40 (d, 1H), 7.16 (dd, 1H), 2.65 (s, 3H).

APCI-MS: *m/z* 254 [MH⁺].

Step III:

4-(Acetylamino)-3-hydroxyphenyl benzoate

To a solution of 2-methyl-1,3-benzoxazol-6-yl benzoate (5.05 g, 20 mmol) in THF (100 mL) a mixture trifluoroacetic acid/water (4 ml/10 mL) was added. The reaction mixture was stirred at room temperature for 16 h, then saturated aqueous NaHCO₃ (150 mL) was added. The mixture was extracted with ethyl acetate (150 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to give the subtitled compound.

¹H-NMR (400 MHz, acetone-d₆): δ 9.76 (br.s, 1H), 9.32 (br.s, 1H), 8.15 (m, 2H), 7.71 (m, 1H), 7.60 (m, 2H), 7.47 (d, 1H), 6.85 (m, 1H), 6.75 (m, 1H), 2.20 (s, 3H).

APCI-MS: *m/z* 272 [MH⁺].

Step IV:

4-(Acetylamino)-3-(((2S)-2-methyloxiran-2-yl)methoxy)phenyl benzoate

This compound was prepared from 4-(acetylamino)-3-hydroxyphenyl benzoate (2.71 g, 10 mmol) and [(2*S*)-2-methyloxiran-2-yl]methyl 3-nitrobenzenesulfonate using the standard procedure and 1-methylpyrrolidin-2-one as a solvent. Flash chromatography on silica gel (ethyl acetate/*n*-heptane) afforded the subtitled compound as a colourless solid (1.31 g, 3.9 mmol, 39 %).

¹H-NMR (400 MHz, CDCl₃): δ 8.41 (d, 1H), 8.18 (m, 2H), 7.91 (br.s, 1H), 7.63 (m, 1H), 7.50 (m, 2H), 6.83 (m, 1H), 4.15 (d, *J* = 10.8 Hz, 1H), 4.03 (d, *J* = 10.8 Hz, 1H), 3.99 (d, *J* = 10.8 Hz, 1H), 2.92 (d, *J* = 4.6 Hz, 1H), 2.78 (d, *J* = 4.6 Hz, 1H), 2.22 (s, 3H), 1.48 (s, 3H).

APCI-MS: *m/z* 342 [MH⁺].

Step V:

N-(2-([(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy)-4-hydroxyphenyl)acetamide trifluoroacetate

A solution of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (20.0 mg, 0.09 mmol) and 4-(acetylamino)-3-([(2*S*)-2-methyloxiran-2-yl]methoxy)phenyl benzoate (30.5 mg, 0.09 mmol) in methanol (2 mL) was refluxed for 3 h. The reaction mixture was cooled to room temperature, and 1 drop of 20 % NaOH in ethanol was added. The mixture was stirred at room temperature for 3 h. The solvent was distilled off under reduced pressure. The residue was purified by HPLC ("Kromasil" column; eluant: [acetonitrile + 0.1 % trifluoroacetic acid (TFA)/water + 0.1 % TFA]) to afford a colourless solid (41 mg, 0.07 mmol, 79 %).

¹H-NMR (400 MHz, acetone-*d*₆): δ 8.67 (br. s, 1H), 7.71 (d, *J* = 7.0 Hz, 1H), 7.22 (s, 1H), 7.12 (dd, *J* = 2.3, 8.5 Hz, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 6.59 (d, *J* = 2.6 Hz, 1H), 6.42 (dd, *J* = 2.6, 8.6 Hz, 1H), 4.03 (d, 1H), 3.97 (d, *J* = 9.7 Hz, 1H), 3.92 (br.s, 1H), 3.82 (br. s, 1H), 3.70 (d, *J* = 13.6 Hz, 1H), 3.52 (m, 3H), 2.1 – 2.5 (m, 4H), 2.10 (s, 3H), 1.51 (s, 3H). APCI-MS: *m/z* 461 [MH⁺].

Example 10

***N*-(5-Chloro-2-{{{(2S)-3-(6-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}phenyl)acetamide**

Step I:

***N*-(5-Chloro-2-hydroxyphenyl)acetamide**

To a suspension of 2-amino-4-chlorophenol (1.43 g, 10.0 mmol) in methanol was added acetic anhydride (0.945 mL, 10.0 mmol) and the reaction mixture was stirred at room temperature for 2 h. The volatiles were removed in vacuo to give the subtitled compound (1.5 g).

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.20 (br.s, 1H); 9.21 (s, 1H); 8.00 (d, *J* = 2.6 Hz, 1H); 6.94 (dd, *J* = 2.6, 8.7 Hz, 1H); 6.84 (d, *J* = 8.7 Hz, 1H); 2.02 (s, 3H).

Step II:

***N*-(5-Chloro-2-[(2S)-oxiran-2-ylmethoxy]phenyl)acetamide**

A mixture of *N*-(5-chloro-2-hydroxyphenyl)acetamide (500 mg, 2.69 mmol), (2S)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (697 mg, 2.69 mmol) and Cs₂CO₃ (1.04 g, 3.22 mmol) in DMF (10 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-50% ethyl acetate in petroleum ether) to give the subtitled compound (600 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 8.47 (d, *J* = 2.3 Hz, 1H); 7.93 (br.s, 1H); 6.98 (dd, *J* = 2.3, 8.7 Hz, 1H); 6.83 (d, *J* = 8.7 Hz, 1H); 4.36 (dd, *J* = 2.4, 11.3 Hz, 1H); 3.94 (dd, *J* = 6.1, 11.3 Hz, 1H); 3.39 (m, 1H); 2.98 (m, 1H); 2.81 (dd, *J* = 2.7, 4.8 Hz, 1H); 2.22 (s, 3H).

APCI-MS: *m/z* 242 (MH⁺).

Step III:

***N*-(5-Chloro-2-{{{(2S)-3-(6-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}phenyl)acetamide**

A mixture of 6-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (26 mg, 0.116 mmol) and *N*-(5-chloro-2-[(2S)-oxiran-2-ylmethoxy]phenyl)acetamide (28 mg, 0.116 mmol) in

ethanol (3 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (28 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 8.18 (d, *J* = 2.4 Hz, 1H); 7.30-7.20 (m, 3H); 7.10-7.00 (m, 2H); 5.02 (s, 2H); 4.23 (m, 1H); 4.14 (dd, *J* = 3.1, 9.9 Hz, 1H); 3.99 (dd, *J* = 6.5, 9.9 Hz, 1H); 2.93 (m, 2H); 2.63 (d, *J* = 6.3 Hz, 2H); 2.55 (m, 2H); 2.21 (s, 3H); 2.00 (m, 2H); 1.73 (m, 2H).

APCI-MS: *m/z* 467 (MH⁺).

Example 11

N-(2-(((2*S*)-3-(6-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl)oxy)-4-fluorophenyl)acetamide

A mixture of 6-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (30 mg, 0.134 mmol) and *N*-{4-fluoro-2-[(2*S*)-oxiran-2-ylmethoxy]phenyl}acetamide (30 mg, 0.134 mmol) in ethanol (3 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (40 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.90 (dd, *J* = 6.2, 8.9 Hz, 1H); 7.29-7.20 (m, 3H); 6.89 (dd, *J* = 2.7, 10.5 Hz, 1H); 6.67 (m, 1H); 5.02 (s, 2H); 4.23 (m, 1H); 4.13 (dd, *J* = 3.1, 9.9 Hz, 1H); 4.01 (dd, *J* = 6.3, 9.9 Hz, 1H); 2.93 (m, 2H); 2.69-2.50 (m, 4H); 2.20 (s, 3H); 2.00 (m, 2H); 1.73 (br.d, *J* = 13.5 Hz, 2H).

APCI-MS: *m/z* 451 (MH⁺).

Example 12

N-(2-(((2*S*)-3-(6-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl)oxy)phenyl)acetamide

A mixture of 6-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (25 mg, 0.111 mmol) and *N*-{2-[(2*S*)-oxiran-2-ylmethoxy]phenyl}acetamide (23 mg, 0.111 mmol) in ethanol (2 mL)

was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (20 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 8.00 (dd, *J* = 1.3, 8.0 Hz, 1H); 7.30-7.20 (m, 3H); 7.12-7.05 (m, 2H); 6.93 (m, 1H); 5.01 (s, 2H); 4.22 (m, 1H); 4.14 (dd, *J* = 3.3, 9.9 Hz, 1H); 4.00 (dd, *J* = 6.4, 9.9 Hz, 1H); 2.94 (m, 2H); 2.69-2.52 (m, 4H); 2.20 (s, 3H); 2.01 (m, 2H); 1.74 (br.d, *J* = 13.5 Hz, 2H).

APCI-MS: *m/z* 433(MH⁺).

Example 13

N-(2-{[(2*S*)-3-(6-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-methoxyphenyl)acetamide

A mixture of 6-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (46 mg, 0.205 mmol) and *N*-{4-methoxy-2[(2*S*)-oxiran-2-ylmethoxy]phenyl}acetamide (48.6 mg, 0.205 mmol) in ethanol (2 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (80 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.75 (d, *J* = 8.9 Hz, 1H); 7.29-7.20 (m, 3H); 6.64 (d, *J* = 2.7 Hz, 1H); 6.51 (dd, *J* = 2.7, 8.9 Hz, 1H); 5.02 (s, 2H); 4.44 (m, 1H); 4.12 (dd, *J* = 3.3, 10.0 Hz, 1H); 3.98 (dd, *J* = 6.2, 10.0 Hz, 1H); 3.80 (s, 3H); 2.96 (m, 2H); 2.68-2.50 (m, 4H); 2.18 (s, 3H); 2.00 (m, 2H); 1.74 (br.d, *J* = 13.2 Hz, 2H).

APCI-MS: *m/z* 461(MH⁺).

Example 14

2-{[(2*S*)-3-(6-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-cyclopropyl-4-fluorobenzamide

A mixture of 6-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (25 mg, 0.111 mmol) and *N*-cyclopropyl-4-fluoro-2-(oxiran-2-ylmethoxy)benzamide (28 mg, 0.111 mmol) in ethanol

was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (32 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.98 (dd, *J* = 6.9, 8.8 Hz, 1H); 7.29-7.20 (m, 3H); 6.98 (dd, *J* = 2.4, 10.8 Hz, 1H); 6.82 (ddd, *J* = 2.4, 8.0, 8.8 Hz, 1H); 5.01 (s, 2H); 4.25 (dd, *J* = 3.1, 9.4 Hz, 1H); 4.19 (m, 1H); 4.11 (dd, *J* = 5.5, 9.4 Hz, 1H); 2.92 (m, 3H); 2.59 (m, 4H); 2.01 (m, 2H); 1.73 (m, 2H); 0.80 (m, 2H); 0.69 (m, 2H).

APCI-MS: *m/z* 477(MH⁺).

10 **Example 15**

N-(2-[(2*S*)-3-(5-Fluoro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]phenyl)acetamide

A mixture of 5-fluoro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (15 mg, 0.072 mmol) and
15 *N*-(2-[(2*S*)-oxiran-2-ylmethoxy]phenyl)acetamide (15 mg, 0.072 mmol) in ethanol (1.5 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (9 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.99 (dd, *J* = 1.2, 8.0 Hz, 1H); 7.18 (dd, *J* = 4.9, 8.0 Hz, 1H); 7.11-6.90 (m, 5H); 5.00 (s, 2H); 4.27 (m, 1H); 4.13 (dd, *J* = 3.2, 9.9 Hz, 1H); 3.99 (dd, *J* = 6.4, 9.9 Hz, 1H); 2.99 (m, 2H); 2.72-2.52 (m, 4H); 2.20 (s, 3H); 2.02 (m, 2H); 1.73 (br.d, *J* = 13.6 Hz, 2H).

APCI-MS: *m/z* 415(MH⁺).

25 **Example 16**

N-(4-Chloro-2-[(2*S*)-2-hydroxy-3-(3-oxo-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy)phenyl)acetamide

Step I:

30 *N*-(4-Chloro-2-hydroxyphenyl)acetamide

To a suspension of 2-amino-5-chlorophenol (1.01g, 7.0 mmol) in methanol (10 mL) was added acetic anhydride (1.08 g, 10.55 mmol) and the reaction mixture was stirred at room temperature for 30 min. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (hexane:ethyl acetate 5:2) to give the subtitled compound (1.19 g).

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.29 (br.s, 1H); 9.26 (br.s, 1H); 7.77 (d, *J* = 8.6 Hz, 1H); 6.86 (d, *J* = 2.4 Hz, 1H); 6.80 (dd, *J* = 2.4, 8.6 Hz, 1H); 2.12 (s, 3H).

APCI-MS: *m/z* 186(MH⁺).

Step II:

N-{4-Chloro-2-[(2*S*)-oxiran-2-ylmethoxy]phenyl}acetamide

To a mixture of (2*S*)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (3.37 g, 13.25 mmol), *N*-(4-chloro-2-hydroxyphenyl)acetamide (2.46g, 17.23 mmol) and Cs₂CO₃ (6.48g, 19.88 mmol) was added DMF (20 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 3h. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (hexane:ethyl acetate 3:2) to give the subtitled compound (2.36 g).

¹H-NMR (CD₃COCD₃, 400 MHz): δ 8.67 (br.s, 1H); 8.30 (d, *J* = 8.7 Hz, 1H); 7.07 (d, *J* = 2.3 Hz, 1H); 6.95 (dd, *J* = 2.2, 8.7 Hz, 1H); 4.46 (dd, *J* = 2.3, 11.5 Hz, 1H); 3.94 (dd, *J* = 6.6, 11.5 Hz, 1H); 3.34 (m, 1H); 2.87 (dd, *J* = 4.3, 5.0 Hz, 1H); 2.73 (dd, *J* = 2.7, 5.0 Hz, 1H); 2.18 (s, 3H).

Step III

N-(4-Chloro-2-{[(2*S*)-2-hydroxy-3-(3-oxo-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide

A mixture of 3*H*-spiro[2-benzofuran-1,4'-piperidin]-3-one (Marxer, A; Rodriguez, H. R; McKenna, J. M; Tsai, H. M., *J. Org. Chem.*, **1975**, *40*, 1427-1433) (61 mg, 0.3 mmol) and *N*-{4-chloro-2-[(2*S*)-oxiran-2-ylmethoxy]phenyl}acetamide (72.5 mg, 0.3 mmol) in ethanol (3 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the

residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (40 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.93 (d, *J* = 7.7 Hz, 1H); 7.84 (m, 2H); 7.71-7.61 (m, 2H); 7.13 (d, *J* = 2.0 Hz, 1H); 7.00 (dd, *J* = 2.0, 8.5 Hz, 1H); 4.58 (m, 1H); 4.13 (m, 2H);
5 3.86 (m, 2H); 3.65-3.45 (m, 4H); 2.64 (m, 2H); 2.20 (s, 3H); 2.06 (m, 2H).

APCI-MS: *m/z* 445(MH⁺).

Example 17

N-Cyclopropyl-2-{[(2*S*)-2-hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}benzamide
10

A mixture 3*H*-spiro[2-benzofuran-1,4'-piperidine] (Marxer, A; Rodriguez, H. R; McKenna, J. M; Tsai, H. M., *J. Org. Chem.*, 1975, 40, 1427-1433) (46.5 mg, 0.246 mmol) and *N*-cyclopropyl-2-[(2*S*)-oxiran-2-ylmethoxy]benzamide (57.4 mg, 0.246 mmol) in
15 ethanol (3 mL) was kept on stirring at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (55 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 8.43 (d, *J* = 1.8 Hz, 1H); 8.20 (dd, *J* = 1.8, 7.8 Hz, 1H); 7.40 (m, 1H); 7.30 (m, 2H); 7.23 (m, 1H); 7.18 (m, 1H); 7.08 (t, *J* = 7.5 Hz, 1H); 6.93 (d, *J*
20 = 8.2 Hz, 1H); 5.10 (s, 2H); 4.20 (m, 2H); 4.00 (dd, *J* = 5.0, 9.3 Hz, 1H); 3.02 (m, 2H); 2.85 (m, 2H); 2.69 (m, 1H); 2.58 (m, 2H); 2.02 (m, 2H); 1.82 (d, 2H); 0.85 (m, 2H); 0.63 (m, 2H).

APCI-MS: *m/z* 423(MH⁺).

Example 18

N-(4-Chloro-2-{[(2*S*)-2-hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide
25

A mixture 3*H*-spiro[2-benzofuran-1,4'-piperidine] (38 mg, 0.2 mmol) and *N*-(4-chloro-2-
30 [(2*S*)-oxiran-2-ylmethoxy]phenyl)acetamide (48.3 mmol) in ethanol (3 mL) was stirred at

80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (35 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 8.05 (d, *J* = 8.7 Hz, 1H); 7.29-7.18 (m, 4H); 7.10 (d, *J* = 2.2 Hz, 1H); 6.94 (dd, *J* = 2.2, 8.7 Hz, 1H); 5.08 (s, 2H); 4.26 (m, 1H); 4.16 (dd, *J* = 3.0, 10.0 Hz, 1H); 4.01 (dd, *J* = 6.4, 9.9 Hz, 1H); 2.97 (m, 2H); 2.69-2.52 (m, 4H); 2.19 (s, 3H); 2.07 (m, 2H); 1.73 (m, 2H).

APCI-MS: *m/z* 433(MH⁺).

Example 19

N-(5-Chloro-2-(((2*S*)-2-hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl)oxy}phenyl)acetamide

A mixture 3*H*-spiro[2-benzofuran-1,4'-piperidine] (63 mg, 0.33 mmol) and *N*-{5-chloro-2-[(2*S*)-oxiran-2-ylmethoxy]phenyl}acetamide (80 mg, 0.33 mmol) in ethanol (5 mL) was stirred at 77 °C for 4h. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in chloroform) to give the titled compound (77 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 8.50 (m, 1H); 7.31 (m, 3H); 7.18 (m, 1H); 6.98 (m, 1H); 6.83 (m, 1H); 5.10 (s, 2H); 4.10 (m, 1H); 4.03 (dd, 1H); 3.91 (dd, 1H); 2.97 (m, 1H); 2.76 (m, 2H); 2.60-2.43 (m, 3H); 2.20 (s, 3H); 2.05-1.89 (m, 2H); 1.60 (m, 2H).

APCI-MS: *m/z* 431(MH⁺).

Example 20

N-(2-(((2*S*)-2-hydroxy-2-methyl-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl)oxy}-4-methoxyphenyl)acetamide

Step I:

[(2*S*)-2-Methyloxiranyl]methyl 3-nitrobenzenesulfonate

To an oven-dried 1000 mL three-necked flask was added powdered activated molecular sieves (8.0 g, 4Å) and CH₂Cl₂ (440 mL), D-(-)-diisopropyl tartrate (4 mL, 14.2 mmol) and 2-methyl-2-propene-1-ol (20 mL, 240 mmol) was added and the mixture was cooled to -20 °C. Titanium tetraisopropoxide (3.5 mL, 11.9 mmol) was added with a few mL of CH₂Cl₂ and the mixture was stirred at -20 °C for 30 min. Cumene hydroperoxide (75 mL, 430 mmol) was added dropwise over 1.5 hours maintaining the temperature at -20 °C. The mixture was stirred at this temperature overnight. Trimethyl phosphite (40 mL, 340 mmol) was added dropwise over 5 hours maintaining the temperature at -20 °C. Triethylamine (50 mL, 360 mmol) and 4-dimethylaminopyridine (DMAP) (3.48 g, 28.5 mmol) was added followed by a solution of 3-nitrobenzenesulphonyl chloride (47 g, 212 mmol) in CH₂Cl₂ (400 mL). The temperature was raised to -10 °C and the mixture was stirred at this temperature overnight. After removing the external cooling vessel, the reaction mixture was filtered through celite. The organic phase was washed with 10% tartaric acid (500 mL), saturated NaHCO₃ (300 mL) and brine (300 mL). The organic layer was dried over magnesium sulphate (MgSO₄) and concentrated in vacuo to give 150 g of a yellow oil. The crude material was purified by silica gel flash chromatography (0-50% ethyl acetate in heptane) to give the subtitled compound (48.8 g).

¹H-NMR (CDCl₃, 400 MHz): δ 8.79-8.75 (m, 1H); 8.52 (ddd, *J* = 1.1, 2.3, 8.3 Hz, 1H); 8.25 (ddd, *J* = 1.1, 1.8, 7.8 Hz, 1H); 7.81 (t, *J* = 8.5 Hz, 1H); 4.28 (d, *J* = 11.3 Hz, 1H); 4.05 (d, *J* = 11.3 Hz, 1H); 2.73 (d, *J* = 4.4 Hz, 1H); 2.67 (d, *J* = 4.4 Hz, 1H); 1.56 (s, 3H).

Step II:

N-(4-Methoxy-2-([(2S)-2-methyloxiran-2-yl]methoxy}phenyl)acetamide

A mixture of [(2S)-2-methyloxiran-2-yl]methyl 3-nitrobenzenesulfonate (2.04 g, 7.46 mmol), *N*-(2-hydroxy-4-methoxyphenyl)acetamide ((1.04 g, 5.74 mmol) and Cs₂CO₃ (2.80 g, 8.61 mmol) in DMF (12 mL) was kept on stirring at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (ethyl acetate : hexane 1:1) to give the subtitled compound (1.19 g).

¹H-NMR (CDCl₃, 400MHz): δ 8.20 (d, *J* = 8.8 Hz, 1H); 7.72 (br.s, 1H); 6.52 (m, 2H); 4.12 (d, *J* = 11.0 Hz, 1H); 3.98 (d, *J* = 11.0 Hz, 1H); 3.77 (s, 3H); 2.91 (d, *J* = 4.7 Hz, 1H); 2.77 (d, *J* = 4.7 Hz, 1H); 2.20 (s, 3H); 1.48 (s, 3H).

5 **Step III:**

N-(2-{[(2*S*)-2-Hydroxy-2-methyl-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide

A mixture of 3*H*-spiro[2-benzofuran-1,4'-piperidine] (57 mg, 0.3 mmol) and *N*-(4-methoxy-2-{[(2*S*)-2-methyloxiran-2-yl]methoxy}phenyl)acetamide (75.4 mg, 0.3 mmol)
10 in ethanol (3 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (70 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.65 (d, *J* = 8.8 Hz, 1H); 7.28-7.15 (m, 4H); 6.61 (d, *J* = 2.7 Hz, 1H); 6.50 (dd, *J* = 2.7, 8.8 Hz, 1H); 5.10 (s, 2H); 3.99 (d, *J* = 9.2 Hz, 1H); 3.90 (d,
15 *J* = 9.2 Hz, 1H); 3.79 (s, 3H); 2.88 (m, 2H); 2.73-2.53 (m, 4H); 2.16 (s, 3H); 2.00 (m, 2H); 1.63 (m, 2H); 1.31 (s, 3H).

APCI-MS: *m/z* 441(MH⁺).

Example 21

20 *N*-[2-{[(2*S*)-2-Hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}-5-(trifluoromethyl)phenyl]acetamide

Step I:

N-[2-[(2*S*)-Oxiran-2-ylmethoxy]-5-(trifluoromethyl)phenyl]acetamide

25 A mixture of *N*-[2-hydroxy-5-(trifluoromethyl)phenyl]acetamide (282 mg, 1.28 mmol), (2*S*)-oxiran-2-ylmethyl-3-nitrobenzenesulfonate (331.5 mg, 1.28 mmol) and Cs₂CO₃ (487.5 mg, 1.28 mmol) in DMF (5 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash

chromatography (0-40% ethyl acetate in petroleum ether) to give the subtitled compound (150 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 8.72 (br.s, 1H); 7.90 (br.s, 1H); 7.31 (m, 1H); 6.97 (d, 1H); 4.46 (dd, *J* = 2.4, 11.3 Hz, 1H); 4.00 (dd, *J* = 6.3, 11.3 Hz, 1H); 3.44 (m, 1H); 3.00 (d, *J* = 4.5 Hz, 1H); 2.80 (dd, *J* = 2.7, 4.8 Hz, 1H); 2.25 (s, 3H).

Step II:

N-[2-[[[(2*S*)-2-Hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy]-5-(trifluoromethyl)phenyl]acetamide

A mixture of 3*H*-spiro[2-benzofuran-1,4'-piperidine] (47.3 mg, 0.25 mmol) and *N*-[2-[(2*S*)-oxiran-2-ylmethoxy]-5-(trifluoromethyl)phenyl]acetamide (69 mg, 0.25 mmol) in ethanol (3 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (38 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 8.49 (d, 1H); 7.39 (dd, 1H); 7.30-7.17 (m, 5H); 5.08 (s, 2H); 4.28 (m, 2H); 4.10 (dd, *J* = 6.5, 9.8 Hz, 1H); 2.98 (m, 2H); 2.68-2.53 (m, 4H); 2.22 (s, 3H); 2.02 (m, 2H); 1.73 (m, 2H).

APCI-MS: *m/z* 465(MH⁺).

Example 22

N-(2-[[[(2*S*)-2-Hydroxy-3-(2-methyl-1'*H*-spiro[indene-1,4'-piperidin]-1'-yl)propyl]oxy]phenyl)acetamide

A mixture of 2-methylspiro[indene-1,4'-piperidine] (Efange, S. M. N; Khare, A. B; Foulon, C; Akella, S. K; Parsons, S. M., *J. Med. Chem.*, **1994**, *37*, 2574-2582) (82.5 mg, 0.35 mmol) and *N*-{2-[(2*S*)-oxiran-2-ylmethoxy]phenyl}acetamide (72.5 mg, 0.35 mmol) in ethanol (3 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (80 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.84 (m, 2H); 7.28 (m, 2H); 7.16 (m, 2H); 7.07 (m, 1H); 6.98 (m, 1H); 6.53 (br.s, 1H); 4.58 (m, 1H); 4.14 (m, 2H); 3.90-3.49 (m, 6H); 2.45 (m, 2H); 2.19 (s, 3H); 1.99 (s, 3H); 1.40 (br.t, *J* = 14.0 Hz, 2H).

APCI-MS: *m/z* 407(MH⁺).

5

Example 23

***N*-(2-([(2*S*)-3-(2,3-Dihydro-1'*H*-spiro[indene-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide**

10 A mixture of 2,3-dihydrospiro[indene-1,4'-piperidine] (Efange, S. M. N; Khare, A. B; Foulon, C; Akella, S. K; Parsons, S. M., *J. Med. Chem.*, 1994, 37, 2574-2582; Chambers, M. S; Baker, R; Billington, D. C; Knight, A. K; Middlemiss, D. N; Wong, E. H. F., *J. Med. Chem.*, 1992, 35, 2033-2039). (78.3 mg, 0.35 mmol) and *N*-{2-[(2*S*)-oxiran-2-ylmethoxy]phenyl}acetamide (72.5 mg, 0.35 mmol) in ethanol (3 mL) was stirred at 80 °C
15 overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (65 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.82 (m, 1H); 7.26-7.12 (m, 5H); 7.06 (m, 1H); 6.98 (m, 1H); 4.50 (m, 1H); 4.10 (d, 2H); 3.72 (m, 2H); 3.45-3.22 (m, 5H); 2.99 (t, *J* = 7.3 Hz, 2H);
20 2.33-2.13 (m, 6H); 1.82 (m, 2H).

APCI-MS: *m/z* 395(MH⁺).

Example 24

***N*-(2-([(2*S*)-2-Hydroxy-3-(2-oxo-1'*H*-spiro[1-benzofuran-3,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide**

25

A mixture of spiro[1-benzofuran-3,4'-piperidin]-2-one (80 mg, 0.28 mmol) and *N*-{2-[(2*S*)-oxiran-2-ylmethoxy]phenyl}acetamide (60 mg, 0.28 mmol) in ethanol (2 mL) was kept on stirring at 80 °C overnight. The volatiles were removed in vacuo and the residue

was purified by high pressure liquid chromatography (HPLC) to give the titled compound (65 mg).

¹H-NMR (DMSO-d₆, 400 MHz): δ 9.03 (br.s, 1H); 7.95-7.90 (m, 1H); 7.44-7.39 (m, 1H); 7.32-7.24 (m, 3H); 7.05 (m, 2H); 6.94 (m, 1H); 6.09 (br.s, 1H); 4.41 (m, 1H); 4.07-3.91 (m, 2H); 3.74-3.36 (m, 8H); 2.31-2.22 (m, 2H); 2.11 (s, 3H).

APCI-MS: m/z 411(MH⁺).

Example 25

2-{{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-cyclopropyl-4-hydroxybenzamide

Step I:

Methyl 2-hydroxy-4-(trityloxy)benzoate

To a solution of methyl 2,4-dihydroxybenzoate (388 mg, 2.0 mmol) in dimethylformamide (5 mL) was added triethylamine, Et₃N, (0.556 mL, 4.0 mmol) followed by trityl chloride (557.5 mg, 2.0 mmol) and 4-dimethylaminopyridine (DMAP) (20 mg). The reaction mixture was kept on stirring at room temperature overnight, poured into a mixture of ice-water, the white precipitate was collected by filtration. This precipitate was subjected to silica gel flash chromatography (0-5% ethyl acetate in petroleum ether) to give the subtitled compound (350 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 10.65 (s, 1H); 7.58-7.22 (m, 16H); 6.38 (m, 2H); 3.89 (s, 3H).

Step II:

***N*-Cyclopropyl-2-hydroxy-4-(trityloxy)benzamide**

Methyl 2-hydroxy-4-(trityloxy)benzoate (340 mg, 0.83 mmol) was dissolved in cyclopropylamine (3 mL) and left at room temperature for a week. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-20% ethyl acetate in petroleum ether) to give the subtitled compound (210 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 12.30 (s, 1H); 7.48 (m, 6H); 7.35-7.22 (m, 9H); 6.92 (d, *J* = 9.0 Hz, 1H); 6.31 (d, *J* = 2.4 Hz, 1H); 6.24 (dd, *J* = 2.4, 8.8 Hz, 1H); 6.08 (br. s, 1H); 2.80 (m, 1H); 0.85 (m, 2H); 0.60 (m, 2H).

5 **Step III:**

***N*-Cyclopropyl-2-[(2*S*)-oxiran-2-ylmethoxy]-4-(trityloxy)benzamide**

A mixture of (2*S*)-oxiran-2-ylmethyl-3-nitrobenzenesulfonate (119 mg, 0.459 mmol), *N*-cyclopropyl-2-hydroxy-4-(trityloxy)benzamide (200 mg, 0.459 mmol) and cesium carbonate, Cs₂CO₃, (186.2 mg, 0.573 mmol) in dimethylformamide (3 mL) was kept on
10 stirring at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate, Na₂SO₄, filtered, concentrated and the residue was purified by silica gel flash chromatography (0-40% ethyl acetate in petroleum ether) to give the subtitled compound (160 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 8.04 (s, 1H); 7.86 (d, *J* = 8.8 Hz, 1H); 7.73 (br. d, *J* = 3.0
15 Hz, 1H); 7.46-7.39 (m, 5H); 7.34-7.23 (m, 9H); 6.44 (dd, *J* = 2.2, 8.8 Hz, 1H); 6.23 (d, *J* = 2.2 Hz, 1H); 4.03 (dd, *J* = 2.7, 10.8 Hz, 1H); 3.68 (dd, *J* = 5.0, 10.8 Hz, 1H); 3.23 (m, 1H); 2.88 (m, 2H); 2.70 (dd, *J* = 2.7, 4.9 Hz, 1H); 0.80 (m, 2H); 0.58 (m, 2H).

Step IV:

20 **2-[[[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-*N*-cyclopropyl-4-hydroxybenzamide**

A mixture of *N*-cyclopropyl-2-[(2*S*)-oxiran-2-ylmethoxy]-4-(trityloxy)benzamide (152 mg, 0.307 mmol) and 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (69 mg, 0.307 mmol) in ethanol (3 mL) was kept on stirring at 80 °C overnight. The volatiles were removed in
25 vacuo and the residue was treated with 80% aqueous acetic acid (10 mL) at reflux for 90 min. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (75 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.83 (d, *J* = 8.4 Hz, 1H); 7.13 (m, 1H); 6.94 (dd, *J* = 2.3,
30 8.4 Hz, 1H); 6.65 (d, *J* = 8.4 Hz, 1H); 6.51-6.45 (m, 2H); 4.21-4.13 (m, 2H); 4.08-4.02 (m,

1H); 3.01 (s, 2H); 2.90 (m, 1H); 2.75 (br.s, 4H); 2.58 (d, $J = 6.2$ Hz, 2H); 1.98 (m, 2H); 1.88 (m, 2H); 0.80 (m, 2H); 0.65 (m, 2H).

APCI-MS: m/z 473(MH^+).

5 **Example 26**

2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy]-*N*-cyclopropyl-4-hydroxybenzamide

Step I:

10 ***N*-Cyclopropyl-2-hydroxy-4-[(4-methoxybenzyl)oxy]benzamide**

Methyl 2-hydroxy-4-[(4-methoxybenzyl)oxy]benzoate (Percec, V; Tomazos, D. *J. Mater. Chem.* 1993, 3, 643-650) (530 mg, 1.83 mmol) was dissolved in cyclopropyl amine (3 mL) and left at room temperature for a week. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-40% ethyl acetate in petroleum
15 ether) to give the subtitled compound (407 mg).

1H -NMR (DMSO- d_6 , 400 MHz): δ 13.20 (br.s, 1H); 8.56 (d, $J = 2.7$ Hz, 1H); 7.72 (d, $J = 8.7$ Hz, 1H); 7.38-7.33 (m, 2H); 6.96-6.92 (m, 2H); 6.49-6.45 (m, 2H); 5.00 (s, 2H); 3.79 (s, 3H); 2.80 (m, 1H); 0.78 (m, 2H); 0.58 (m, 2H).

20 **Step II:**

[(2S)-2-Methyloxiranyl]methyl 3-nitrobenzenesulfonate

To an oven-dried 1000 mL three-necked flask was added powdered activated molecular sieves (8.0 g, 4Å) and dichloromethane, CH_2Cl_2 , (440 mL), D-(-)-diisopropyl tartrate (4 mL, 14.2 mmol) and 2-methyl-2-propene-1-ol (20 mL, 240 mmol) was added and the
25 mixture was cooled to $-20^\circ C$. Titanium tetraisopropoxide (3.5 mL, 11.9 mmol) was added with a few mL of dichloromethane and the mixture was stirred at $-20^\circ C$ for 30 min. Cumene hydroperoxide (75 mL, 430 mmol) was added dropwise over 1.5 hours maintaining the temperature at $-20^\circ C$. The mixture was stirred at this temperature overnight. Trimethyl phosphite (40 mL, 340 mmol) was added dropwise over 5 hours
30 maintaining the temperature at $-20^\circ C$. Triethyl amine (50 mL, 360 mmol) and

4-dimethylaminopyridine (DMAP) (3.48 g, 28.5 mmol) was added followed by a solution of 3-nitrobenzenesulphonyl chloride (47 g, 212 mmol) in dichloromethane (400 mL). The temperature was raised to -10°C and the mixture was stirred at this temperature overnight. After removing the external cooling vessel, the reaction mixture was filtered through celite. The organic phase was washed with 10% tartaric acid (500 mL), saturated sodium hydrogencarbonate, NaHCO_3 , (300 mL) and brine (300 mL). The organic layer was dried over magnesium sulphate, MgSO_4 , and concentrated in vacuo to give 150 g of a yellow oil. The crude material was purified by silica gel flash chromatography (0-50% ethyl acetate in heptane) to give the subtitled compound (48.8 g).

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 8.79-8.75 (m, 1H); 8.52 (ddd, $J = 1.1, 2.3, 8.3$ Hz, 1H); 8.25 (ddd, $J = 1.1, 1.8, 7.8$ Hz, 1H); 7.81 (t, $J = 8.5$ Hz, 1H); 4.28 (d, $J = 11.3$ Hz, 1H); 4.05 (d, $J = 11.3$ Hz, 1H); 2.73 (d, $J = 4.4$ Hz, 1H); 2.67 (d, $J = 4.4$ Hz, 1H); 1.56 (s, 3H).

Step III:

N-Cyclopropyl-4-[(4-methoxybenzyl)oxy]-2-[(2S)-2-methloxiran-2-yl]methoxy}benzamide

A mixture of [(2S)-2-methyloxiran-2-yl]methyl 3-nitrobenzenesulfonate (218 mg, 0.797 mmol), *N*-cyclopropyl-2-hydroxy-4-[(4-methoxybenzyl)oxy]benzamide (250 mg, 0.797 mmol) and cesium carbonate, Cs_2CO_3 , (311 mg, 0.956 mmol) in dimethylformamide (5 mL) was kept on stirring at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate, Na_2SO_4 , filtered, concentrated and the residue was purified by silica gel flash chromatography (0-40% ethyl acetate in petroleum ether) to give the subtitled compound (260 mg).

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 8.19 (d, $J = 8.8$ Hz, 1H); 7.90 (d, $J = 3.0$ Hz, 1H); 7.38-7.33 (m, 2H); 6.96-6.92 (m, 2H); 6.70 (dd, $J = 2.3, 8.8$ Hz, 1H); 6.48 (d, $J = 2.3$ Hz, 1H); 5.02 (s, 2H); 4.14 (d, $J = 10.3$ Hz, 1H); 4.06 (d, $J = 10.3$ Hz, 1H); 3.80 (s, 3H); 3.04-2.98 (m, 1H); 2.94 (d, $J = 4.7$ Hz, 1H); 2.87 (d, $J = 4.7$ Hz, 1H); 1.50 (s, 3H); 0.86 (m, 2H); 0.65 (m, 2H).

APCI-MS: m/z 384(MH^+).

Step IV:

2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy]-*N*-cyclopropyl-4-[(4-methoxybenzyl)oxy]benzamide

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (70 mg, 0.313 mmol) and *N*-cyclopropyl-4-[(4-methoxybenzyl)oxy]-2-[[[(2S)-2-methoxiran-2-yl]methoxy]benzamide (120 mg, 0.313 mmol) in ethanol (3 mL) was kept on stirring at 80 °C for 6h. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.2% ammonium hydroxide, NH₄OH) to give the subtitled compound (100 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 8.22-8.15 (m, 2H); 7.39-7.34 (m, 2H); 7.13-7.06 (m, 2H); 6.97-6.92 (m, 2H); 6.72-6.66 (m, 2H); 6.50 (d, *J* = 2.3 Hz, 1H); 5.08 (s, 2H); 3.88 (s, 3H); 3.05 (m, 1H); 2.99 (s, 2H); 2.90 (m, 2H); 2.75 (m, 1H); 2.66 (d, *J* = 13.8 Hz, 1H); 2.64 (m, 1H); 2.49 (d, *J* = 13.8 Hz, 1H); 1.99 (m, 2H); 1.82 (m, 2H); 1.60 (br.s, 2H); 1.33 (s, 3H); 0.86 (m, 2H); 0.65 (m, 2H).

APCI-MS: *m/z* 607(MH⁺).

Step V:

2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy]-*N*-cyclopropyl-4-hydroxybenzamide

2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy]-*N*-cyclopropyl-4-[(4-methoxybenzyl)oxy]benzamide (80 mg, 0.131 mmol) was treated with 10% trifluoroacetic acid in dichloromethane (10 mL) at room temperature for 15 min. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% ammonium hydroxide, NH₄OH) to give the titled compound (40 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.83 (m, 1H); 7.12 (m, 1H); 7.03 (dd, *J* = 2.3, 8.5 Hz, 1H); 6.64 (d, *J* = 8.5 Hz, 1H); 6.49-6.45 (m, 2H); 4.09 (d, *J* = 9.2 Hz, 1H); 3.90 (d, *J* = 9.2 Hz, 1H); 2.99 (s, 2H); 2.92 (m, 1H); 2.79 (m, 2H); 2.66 (m, 2H); 2.58 (d, *J* = 13.9 Hz, 1H); 2.50 (d, *J* = 13.9 Hz, 1H); 1.93-1.75 (m, 4H); 1.31 (s, 3H); .80 (m, 2H); 0.68 (m, 2H).

APCI-MS: m/z 487(MH^+).

Example 27

N-(4-hydroxy-2-(((2*S*)-2-hydroxy-3-(1'*H*,4*H*-spiro[chromene-3,4'-piperidin]-1'-yl)propyl)oxy}phenyl)acetamide

Step I

(1*Z*)-1-(2,4-dihydroxyphenyl)ethanone oxime

1-(2,4-dihydroxyphenyl)ethanone (4.5 g, 29.6 mmol) was dissolved in pyridin (17 mL). Hydroxylamine hydrochloride (2.1 g, 29.6 mmol) was added in small portions over 10 minutes. After stirring at room temperature over night the green-yellowish solution was partitioned between water and ethyl acetate. The organic phase was washed twice with water and once with 0.2 M hydrochloric acid, and was finally concentrated. The oily residue was treated with water, evaporated to yield a white semi solid residue, which was treated with toluene and evaporated to give the titled compound (4.8 g, 98%) as a white solid.

Step II

2-methyl-1,3-benzoxazol-6-ol

To a cooled (5°C) solution of (1*Z*)-1-(2,4-dihydroxyphenyl)ethanone oxime (9.7 g, 57.7 mmol) in acetonitrile (65 mL) and dimethylacetamide (11 mL) was added phosphorus oxychloride (5.6 mL, 60.3 mmol) drop wise. The temperature was not allowed to exceed 10°C during the addition. After 1 hrs stirring at room temperature the yellow slurry was poured on a mixture of sodium hydrogen carbonate and ice. The resulting precipitate was filtered off and dried yielding 6.3 g (73%) the titled compound.

Step III

2-methyl-1,3-benzoxazol-6-yl acetate

A slurry of 2-methyl-1,3-benzoxazol-6-ol (7.1 g, 47.8 mmol) in tetrahydrofuran was cooled to 10°C and triethylamine (5.8 mL, 81.3 mmol) was added in one portion, followed by the addition of acetyl chloride (11.3 mL, 81.6 mmol) in small portions. After stirring at room temperature over night the reaction mixture was partitioned between water and ethyl

acetate. The organic phase was washed twice with water and concentrated to give the titled compound (8.2 g, 90%) as a beige solid.

Step IV

4-(acetylamino)-3-hydroxyphenyl acetate

2-methyl-1,3-benzoxazol-6-yl acetate (8.1 g, 42.3 mmol) was dissolved in tetrahydrofuran (60 mL), and trifluoroacetic acid (4 mL, 53.2 mmol) was added. The light brown solution was stirred over night at room temperature. Sodium hydrogen carbonate (aq, sat) was added, and the solution was extracted twice with ethyl acetate. The combined organic layers were concentrated to the titled compound (8.0 g, 91%) as a beige solid.

Step V

4-(acetylamino)-3-[(2*S*)-oxiran-2-ylmethoxy]phenyl acetate

A solution of 4-(acetylamino)-3-hydroxyphenyl acetate (669 mg, 3.2 mmol), (2*S*)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (748 mg, 2.9 mol) and caesium carbonate (1.05 g, 3.2 mmol) in 1-methyl-pyrrolidinone (10 mL) was stirred over night at room temperature, and then partitioned between water and ethyl acetate. The organic phase was washed twice with water and concentrated to an yellow oil, which was suspended in methanol/diethyl ether, 1/2. The precipitated beige solid was filtered off and dried to give the titled compound (296 mg, 38%).

Step VI

N-(4-hydroxy-2-[[[(2*S*)-2-hydroxy-3-(1'*H*,4*H*-spiro[chromene-3,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide

A solution of 4-(acetylamino)-3-[(2*S*)-oxiran-2-ylmethoxy]phenyl acetate (56 mg, 0.21 mmol) and 4*H*-spiro[chromene-3,4'-piperidine] (43 mg, 0.21 mmol) in methanol (1 mL) was stirred over night at 60°C, and then concentrated. The dark grey residue was purified by HPLC on C18 ("Kromasil" column, 5 um, acetonitrile/water 10/90 to 60/40 over 20 min with 0.1% trifluoroacetic acid) to give the title compound (39 mg, 33%) trifluoroacetate salt.

¹H-NMR (acetone-d₆, 400 MHz,) δ: 11.27 (1H, bs); 8.52 (1H, bs); 7.95 (1H, d); 7.10 (2H, t); 6.86 (1H, t); 6.78 (1H,d); 6.53 (1H, d); 6.40 (1H, dd); 4.55-4.48 (1H, m); 4.21 (1H, s);

4.09-4.01 (2H, m); 3.91 (1H, s); 3.83-3.65 (2H, m); 3.65-3.49 (2H, m); 3.49-3.35 (2H, m); 3.00 (1H, s); 2.70 (1H, s); 2.08 (3H, s); 2.02-1.74 (4H, m)

APCI-MS: m/z 427 [MH⁺]

5 **Example 28**

2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy]-4-hydroxy-*N*-methylbenzamide (trifluoroacetate)

Step I:

10 **2-Hydroxy-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide**

To a suspension of methyl 2-hydroxy-4-[(4-methoxybenzyl)oxy]benzoate (500 mg, 1.73 mmol) in methanol (15 mL) was slowly added aqueous 40% methylamine (3 mL) at 0 °C. After addition was complete the reaction mixture was kept on stirring at room temperature for 2 days. The volatiles were removed in vacuo to give the subtitled compound (500 mg).

15 ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 13.20 (br.s, 1H); 8.60 (m, 1H); 7.70 (d, *J* = 8.8 Hz, 1H); 7.35 (m, 2H); 6.96-6.92 (m, 2H); 6.50 (dd, *J* = 2.6, 8.8 Hz, 1H); 6.42 (d, *J* = 2.6 Hz, 1H); 5.04 (s, 2H); 3.76 (s, 3H); 2.79 d, *J* = 4.6 Hz, 3H).

APCI-MS: m/z 288(MH⁺).

20 **Step II:**

4-[(4-Methoxybenzyl)oxy]-*N*-methyl-2-[[[(2S)-2-methyloxiran-2-yl]methoxy]benzamide

A mixture of [(2S)-2-methyloxiran-2-yl]methyl 3-nitrobenzenesulfonate (133 mg, 0.487 mmol), 2-hydroxy-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide (140 mg, 0.487 mmol) and cesium carbonate, Cs₂CO₃, (198 mg, 0.608 mmol) in dimethylformamide (5 mL) was
25 kept on stirring at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate, Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-60% ethyl acetate in petroleum ether) to give the subtitled compound
30 (130 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 8.18 (d, *J* = 8.8 Hz, 1H); 7.82 (m, 1H); 7.37 (m, 2H); 6.97-6.92 (m, 2H); 6.71 (dd *J* = 2.3, 8.8 Hz, 1H); 6.53 (d, *J* = 2.3 Hz, 1H); 5.01 (s, 2H); 4.18 (d, *J* = 10.5 Hz, 1H); 4.10 (d, *J* = 10.5 Hz, 1H); 3.85 (s, 3H); 3.02 (d, *J* = 4.9 Hz, 3H); 2.97 (d, *J* = 4.6 Hz, 1H); 2.80 (d, *J* = 4.6 Hz, 1H); 1.50 (s, 3H).

5 APCI-MS: *m/z* 358(MH⁺).

Step III:

2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy]-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide

10 A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (70 mg, 0.313 mmol) and 4-[(4-methoxybenzyl)oxy]-*N*-methyl-2-[[[(2S)-2-methyloxiran-2-yl]methoxy]benzamide (112 mg, 0.313 mmol) in ethanol (2 mL) was kept on stirring at 80 °C for 4.5 h. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% ammonium hydroxide, NH₄OH) to give the subtitled compound (135 mg).

15 ¹H-NMR (CDCl₃, 400 MHz): δ 8.18 (d, *J* = 8.7 Hz, 1H); 8.12 (m, 1H); 7.39-7.35 (m, 2H); 7.12 (m, 2H); 7.08 (dd, *J* = 2.3, 8.5 Hz, 1H); 6.97-6.92 (m, 2H); 6.72-6.66 (m, 2H); 6.52 (d, *J* = 2.3 Hz, 1H); 5.05 (s, 2H); 3.90 (m, 2H); 3.82 (s, 3H); 3.0 (d, *J* = 4.9 Hz, 3H); 2.98 (s, 2H); 2.94-2.84 (m, 2H); 2.73 (m, 1H); 2.69 (d, *J* = 13.9 Hz, 1H); 2.63 (m, 1H); 2.49 (d, 20 *J* = 13.9 Hz, 1H); 1.99 (m, 2H); 1.82 (m, 2H).

APCI-MS: *m/z* 581(MH⁺).

Step IV:

2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy]-4-hydroxy-*N*-methylbenzamide (trifluoroacetate)

25 2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy]-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide (125 mg, 0.215 mmol) was treated with 10% trifluoroacetic acid in dichloromethane (10 mL) at room temperature for 20 min. The volatiles were removed in vacuo and the residue was purified by HPLC

(acetonitrile/water (CH₃CN/H₂O), 0.1% trifluoroacetic acid) to give the titled compound (50 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.52-7.47 (m, 1H); 7.20 (br.s, 1H); 7.10 (dd, *J* = 2.3, 8.5 Hz, 1H); 6.75 (d, *J* = 8.5 Hz, 1H); 6.52 (br.s, 1H); 6.49 (dd, *J* = 2.1, 8.5 Hz, 1H); 4.20 (m, 2H); 4.00 (m, 1H); 3.62-3.35 (m, 4H); 3.18 (2xs, 2H); 3.90 (2xs, 3H); 2.60 (m, 2H); 2.32-2.05 (m, 3H); 1.39 (s, 3H).

APCI-MS: *m/z* 461(MH⁺).

Example 29

2- $\{[(2S)$ -3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy]oxy}-4-hydroxy-*N*-methylbenzamide

Step I:

4-[4-Methoxybenzyl]oxy]-*N*-methyl-2-[(2*S*)-oxiran-2-ylmethoxy]benzamide

A mixture of (2*S*)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (151 mg, 0.584 mmol), methyl 2-hydroxy-4-[(4-methoxybenzyl)oxy]benzoate (168 mg, 0.584 mmol) and cesium carbonate, Cs₂CO₃, (228 mg, 0.70 mmol) in dimethylformamide (4 mL) was kept on stirring at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate, Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-90% ethyl acetate in petroleum ether) to give the subtitled compound (150 mg).

¹H-NMR (DMSO-*d*₆, 400 MHz): δ 7.90 (m, 1H); 7.75 (d, *J* = 8.7 Hz, 1H); 7.37 (d, *J* = 8.6 Hz, 2H); 6.96-6.91 (m, 2H); 6.74 (d, *J* = 2.3 Hz, 1H); 6.68 (dd, *J* = 2.3, 8.7 Hz, 1H); 5.08 (s, 2H); 4.48 (dd, *J* = 2.5, 11.5 Hz, 1H); 4.04 (dd, *J* = 6.0, 11.5 Hz, 1H); 3.78 (s, 3H); 3.45 (m, 1H); 2.86 (t, *J* = 4.9 Hz, 1H); 2.79 (d, *J* = 4.7 Hz, 3H); 2.73 (dd, *J* = 2.7, 5.0 Hz, 1H).

APCI-MS: *m/z* 344(MH⁺).

Step II:

2- $\{[(2S)$ -3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (70 mg, 0.313 mmol) and 4-[4-methoxybenzyl]oxy]-*N*-methyl-2-[(2*S*)-oxiran-2-ylmethoxy]benzamide (107.5 mg, 0.313 mmol) in ethanol (3 mL) was kept on stirring at 80 °C for 6h. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.2% ammonium hydroxide, NH₄OH) to give the subtitled compound (122 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 8.18 (d, *J* = 8.8 Hz, 1H); 8.10 (m, 1H); 7.34 (d, *J* = 8.7 Hz, 2H); 7.14 (br.s, 1H); 7.08 (m, 1H); 6.95 (d, *J* = 8.7 Hz, 2H); 6.70 (m, 2H); 6.55 (d, *J* = 2.1 Hz, 1H); 5.08 (s, 2H); 4.22-4.12 (m, 2H); 3.98 (dd, *J* = 5.3, 9.3 Hz, 1H); 3.85 (s, 3H); 3.01 (s, 2H); 3.00 (d, *J* = 4.8 Hz, 3H); 2.95-2.87 (m, 1H); 2.80 (m, 1H); 2.65-2.50 (m, 4H); 2.01 (m, 2H); 1.82 (m, 2H).

APCI-MS: *m/z* 567(MH⁺).

Step III:

2-{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy]oxy}-4-hydroxy-*N*-methylbenzamide

2-{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide (110 mg, 0.194 mmol) was treated with 10% trifluoroacetic acid in dichloromethane (10 mL) at room

temperature for 20 min. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% ammonium hydroxide, NH₄OH) to give the titled compound (45 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.81 (d, *J* = 8.7 Hz, 1H); 7.13 (m, 1H); 7.04 (dd, *J* = 2.3, 8.5 Hz, 1H); 6.66 (d, *J* = 8.5 Hz, 1H); 6.52 (d, *J* = 2.2 Hz, 1H); 6.48 (dd, *J* = 2.2, 8.6 Hz, 1H); 4.25-4.17 (m, 2H); 4.05 (m, 1H); 3.02 (s, 2H); 2.92 (s, 3H); 2.70 (br.s, 4H); 2.60 (d, *J* = 6.2 Hz, 2H); 1.94 (m, 2H); 1.84 (m, 2H).

APCI-MS: *m/z* 447(MH⁺).

Example 30

***N*-(2-([(2*S*)-3-(5-Chloro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-hydroxyphenyl)acetamide trifluoroacetate**

Step I:

5 **Ethyl 5-chloro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidine]-1'-carboxylate**

A mixture of ethyl 4-oxopiperidine-1-carboxylate (1.71 g, 10 mmol), 4-chlorobenzene-1,2-diol (1.73 g, 12 mmol), and a catalytic amount of 4-methylbenzenesulfonic acid hydrate in dry toluene (30 ml) were refluxed with water separator for 7 h. After cooling, the reaction mixture was washed with 2N sodium hydroxide (2 x 25 ml), and the solvent was removed
10 in vacuo. Flash chromatography on silica gel (heptane/ethyl acetate, 2 : 1) of the residual semi-solid product afforded ethyl 5-chloro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidine]-1'-carboxylate as colourless crystals (0.43 g, 15 %).

APCI-MS: *m/z* 298 [*MH*⁺].

¹H-NMR (400MHz, CDCl₃): δ 6.77 (m, 2H), 6.67 (m, 1H), 4.16 (q, 2H, *J* = 7.1 Hz), 3.67
15 (t, 4H, *J* = 5.7 Hz), 1.98 (t, 4H, *J* = 5.7 Hz), 1.28 (t, 3H, *J* = 7.1 Hz).

Step II:

5-Chlorospiro[1,3-benzodioxole-2,4'-piperidine]

Ethyl 5-chloro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidine]-1'-carboxylate (0.43 g, 1.45
20 mmol) was dissolved in ethanol (5 ml) and water (0.4 ml). Sodium hydroxide (0.2 g) was added followed by reflux for 2 days. After cooling, the solution was concentrated in vacuo, and acidified with 10 % HCl to pH < 1. After the gas evolution had ceased, the solution was made alkaline by addition of saturated aqueous sodium hydrogencarbonate, NaHCO₃, and extracted with dichloromethane. Drying with sodium sulphate, Na₂SO₄, and
25 evaporation of the solvent afforded a colourless solid (0.28 g, 1.2 mol, 86 %).

APCI-MS: *m/z* 226 [*MH*⁺].

¹H-NMR (400MHz, CDCl₃): δ 6.6 – 6.9 (m, 3H), 3.06 (t, 4H, *J* = 5.0 Hz), 1.99 (t, 4H, *J* =
5.2 Hz).

30 **Step III:**

***N*-(2-{[(2*S*)-3-(5-Chloro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)acetamide trifluoroacetate**

A solution of 5-chlorospiro[1,3-benzodioxole-2,4'-piperidine] (45 mg, 0.2 mmol) and 4-(acetylamino)-3-[(2*S*)-oxiran-2-ylmethoxy]phenyl acetate (53 mg, 0.2 mmol) in methanol (5 ml) was refluxed for 15 h. The solvent was distilled off under reduced pressure. The residue was purified by preparative HPLC ("Kromasil" column; eluent: [acetonitrile + 0.1 % trifluoroacetic acid (TFA)/water + 0.1 % TFA]) to afford the titled compound as a colourless solid (37 mg, 0.07 mmol, 33 %).

APCI-MS: *m/z* 449 [MH⁺].

¹H-NMR (400MHz, acetone-d₆): δ 8.47 (br. s, 1H), 7.93 (d, 1H, *J* = 8.7 Hz), 6.8 – 7.0 (m, 3H), 6.53 (d, 1H, *J* = 2.6 Hz), 6.41 (dd, 1H, *J* = 2.6 Hz, *J* = 8.7 Hz), 4.54 (m, 1H), 4.08 (m, 2H), 3.66 (m, 2H), 2.51 (m, 4H), 2.08 (s, 3H), 2.06 (m, 4H).

Example 31

***N*-(2-{[(2*S*)-3-(5-Chloro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-4-hydroxyphenyl)acetamide trifluoroacetate**

The title compound was prepared as described in Example 9 from 5-chlorospiro[1,3-benzodioxole-2,4'-piperidine] (45 mg, 0.2 mmol) and 4-(acetylamino)-3-[(2*S*)-2-methyloxiran-2-yl]methoxy}phenyl benzoate (68 mg, 0.2 mmol) as a colourless solid (30 mg, 0.05 mmol, 26 %).

APCI-MS: *m/z* 463 [MH⁺].

¹H-NMR (400MHz, acetone-d₆): δ 8.59 (br. s, 1H), 7.73 (d, 1H, *J* = 8.7 Hz), 6.8 – 7.0 (m, 3H), 6.58 (d, 1H, *J* = 2.6 Hz), 6.42 (dd, 1H, *J* = 2.6 Hz, *J* = 8.7 Hz), 4.42 (d, 1H, *J* = 9.7 Hz), 3.97 (d, 1H, *J* = 9.7 Hz), 3.71 (d, 1H, *J* = 14 Hz), 3.54 (d, 1H, *J* = 14 Hz), 2.52 (m, 4H), 2.09 (s, 3H), 2.06 (m, 4H), 1.51 (s, 3H).

Example 32

***N*-(4-Hydroxy-2-{[(2*S*)-2-hydroxy-3-(1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide trifluoroacetate**

The title compound was prepared from spiro[1,3-benzodioxole-2,4'-piperidine] (E. K. Moltzen, J. Perrengaard, E. Meier, *J. Med. Chem.* 1995, 38 (11), 2009 – 2007) (38 mg, 0.2 mmol) as described Example 30. Yield 78 mg, 0.15 mmol, 74 %.
APCI-MS: m/z 415 [MH⁺].

5 ¹H-NMR (400MHz, acetone-d₆): δ 7.90 (d, 1H, *J* = 8.7 Hz), 6.87 (s, 4H), 6.53 (d, 1H, *J* = 2.6 Hz), 6.75 (dd, 1H, *J* = 2.6 Hz, *J* = 8.7 Hz), 4.56 (m, 1H,), 4.08 (m, 2H), 3.69 (m, 2H), 2.46 (m, 4H), 2.09 (s, 3H), 2.07 (m, 4H).

Example 33

10 ***N*-(4-Hydroxy-2-([(2*S*)-2-hydroxy-2-methyl-3-(1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)propyl]oxy)phenyl)acetamide trifluoroacetate**

The title compound was prepared from spiro[1,3-benzodioxole-2,4'-piperidine] (38 mg, 0.2 mmol) as described in Example 9. Yield 88 mg, 0.16 mmol, 81 %.

APCI-MS: m/z 429 [MH⁺].

15 ¹H-NMR (400MHz, acetone-d₆): δ 7.68 (d, 1H, *J* = 8.7 Hz), 6.86 (s, 4H), 6.60 (d, 1H, *J* = 2.5 Hz), 6.43 (dd, 1H, *J* = 2.6 Hz, *J* = 8.7 Hz), 4.06 (d, 1H, *J* = 9.7 Hz), 3.98 (d, 1H, *J* = 9.7 Hz), 4.03 (d, 1H, *J* = 9.7 Hz), 3.77 (d, 1H, *J* = 13.6 Hz), 3.60 (d, 1H, *J* = 13.6 Hz), 2.51 (m, 4H), 2.10 (s, 3H), 2.08 (m, 4H), 1.52 (s, 3H).

20 **Intermediate Compound: 5-Chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine]**

Step I:

1'-Benzyl-5-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidin]-3-one

To a solution of 2-bromo-5-chlorobenzoic acid (2.35 g, 10.0 mmol) in tetrahydrofuran (THF) (15 mL) was added, a 1.6 M solution in hexane, *n*-butyllithium (20 mL, 32.0 mmol)
25 slowly at –78 °C under nitrogen. After addition was complete the reaction mixture was kept on stirring at –78 °C for 3 h. Then a solution of 1-benzylpiperidin-4-one (3.78 g, 20.0 mmol) in THF (10 mL) was added slowly to the reaction mixture at –78 °C. After addition was complete the reaction temperature was raised to room temperature and the reaction
30 mixture was kept on stirring at room temperature overnight. The reaction mixture was

poured into a mixture of water (60 mL) and diethyl ether (60 mL), layers were separated. The aqueous layer was extracted with diethyl ether (2 x 20 mL). The aqueous layer was acidified with aqueous 6M hydrochloric acid (HCl) to pH 2 and boiled for 1 h, cooled to 0 °C, pH was adjusted to 10.0 by addition of aqueous sodium hydroxide (NaOH) (6M) and rapidly extracted with trichloromethane (CHCl₃). The organic layer was washed with water, dried over sodium sulphate (Na₂SO₄), filtered and concentrated in vacuo to give the subtitled compound (1.22 g) and it was pure enough for the next step.

¹H-NMR (CDCl₃, 400 MHz): δ 7.85 (m, 1H); 7.65 (dd, *J* = 1.9, 8.2 Hz, 1H); 7.41-7.26-1.69 (m, 2H).

APCI-MS: *m/z* 328(MH⁺).

Step II:

1'-Benzyl-5-chloro-3H-spiro[2-benzofuran-1,4'-piperidine]

To a solution of 1'-benzyl-5-chloro-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (1.1 g, 3.35 mmol) in THF (12 mL) was added 1 M solution of borane complex in THF (7 mL, 7.0 mmol) slowly at 0 °C. After addition was complete reaction mixture was kept at room temperature for 30 min, then kept at reflux overnight, cooled to 0 °C and 6M aqueous HCl (3.5 mL) was added slowly. The reaction mixture was kept at reflux for 5h, cooled to 0 °C, pH of the reaction mixture was adjusted to 10 by addition of aqueous NaOH (6M) and the whole was extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulphate (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by silica gel flash chromatography (0-30% ethyl acetate in petroleum ether) to give the subtitled compound (1.0 g).

¹H-NMR (CDCl₃, 400 MHz): δ 7.40-7.06 (m, 8H); 5.03 (s, 2H); 3.60 (s, 2H), 2.87 (m, 2H); 2.45 (m, 2H); 1.95 (m, 2H); 1.80 (m, 2H).

APCI-MS: *m/z* 314(MH⁺).

Step III:

5-Chloro-3H-spiro[2-benzofuran-1,4'-piperidine]

To a solution of 1'-benzyl-5-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (950 mg, 3.02 mmol) in dichloromethane (CH₂Cl₂) (6 mL) was added chloroethyl chloroformate (560.6 mg, 3.92 mmol) slowly at 0 °C. After addition was complete the reaction mixture was kept on stirring at 0 °C for 25 min. The volatiles were removed in vacuo, the residue was dissolved in methanol (6 mL) and kept at reflux for 40 min. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-5% methanol in dichloromethane, 0.2% ammonium hydroxide, NH₄OH) to give the titled compound (300 mg) and 1'-benzyl-5-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidin] was recovered (320 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.28-7.24 (m, 2H); 7.18-7.13 (m, 1H); 5.00 (s, 2H); 2.95 (m, 4H); 1.90-1.77 (m, 2H); 1.72-1.63 (m, 2H).
APCI-MS: m/z 224(MH⁺).

Intermediate Compound: 5-Fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine]

Step I:

1'-Benzyl-5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine]

To a stirring suspension of magnesium strip (763 mg) in diethyl ether (7 mL) was added a crystal of iodine followed by 0.4 mL of 2-(bromomethyl)-1,4-difluorobenzene under nitrogen. The reaction was initiated with a high intensity heat gun, then 2-(bromomethyl)-1,4-difluorobenzene (5.0 g, 24.25 mmol) in diethyl ether (7 mL) was added at such a rate that a gentle reflux was maintained. After addition was complete the reaction mixture was kept on stirring at reflux for 100 min, cooled to room temperature. To this reaction mixture a solution of 1-benzylpiperidin-4-one (4.57 g, 24.25 mmol) in diethyl ether (12 mL) was added dropwise with vigorous stirring. After addition was complete a white cake was formed which was left overnight at room temperature. The cake was hydrolized by treatment with aqueous ammonium chloride (NH₄Cl) solution, extracted with diethyl ether. The organic layer was washed with water, dried over sodium sulphate (Na₂SO₄), filtered, concentrated and the residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.1% ammonium hydroxide, NH₄OH) to give intermediate

compound 1-benzyl-4-(2,5-difluorobenzyl)piperidin-4-ol (2.74 g) containing large amount of impurities. To a suspension of sodium hydride (NaH) (55%, 1.12 g, 26.0 mmol) in toluene (10 mL) was slowly added a solution of 1-benzyl-4-(2,5-difluorobenzyl)piperidin-4-ol in toluene (15 mL). After addition was complete, the reaction mixture was kept on stirring at 110 °C (in a preheated oil bath), after 5 minutes dimethylformamide (9 mL) was added and stirring was continued at reflux for 2h. The reaction mixture was cooled to room temperature, water (20 mL) was added and extracted with ethyl acetate. The organic layer was dried over sodium sulphate (Na₂SO₄), filtered, concentrated and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.1% ammonium hydroxide, NH₄OH) to give the subtitled compound (190 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 7.39-7.26 (m, 5H); 6.88-6.76 (m, 2H); 6.67 (dd, *J* = 4.2, 8.7 Hz, 1H); 3.59 (s, 2H); 2.99 (s, 2H); 2.68-2.47 (m, 4H); 2.03-1.94 (m, 2H); 1.86-1.76 (m, 2H).

APCI-MS: *m/z* 298(MH⁺).

Step II:

5-Fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine]

Ethyl chloroformate (65.6mg, 0.604 mmol) was added to a solution of 1'-benzyl-5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (150 mg, 0.504 mmol) in toluene (2 mL) and the reaction mixture was refluxed overnight. The reaction mixture was cooled to room temperature, diluted by addition of toluene, washed successively with aqueous sodium hydrogencarbonate (NaHCO₃) and water. The organic layer was dried over sodium sulphate (Na₂SO₄) filtered and concentrated in vacuo. The residue was dissolved in ethanol (3.5 mL), aqueous potassium hydroxide (KOH) (800mg KOH in 0.8 mL water) was added and the reaction mixture was kept on stirring at reflux overnight, cooled to room temperature, extracted with ethyl acetate. The organic layer was well washed with water, dried over sodium sulphate (Na₂SO₄), filtered and concentrated. The residue was purified by HPLC (10% acetonitrile (CH₃CN)-55% CH₃CN in water containing 0.1% ammonium hydroxide, NH₄OH) to give the titled compound (49 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 6.92-6.87 (m, 1H); 6.81-6.75 (m, 1H); 6.64 (dd, *J* = 4.2, 8.7 Hz, 1H); 3.08-2.98 (m, 4H); 2.89-2.81 (m, 2H); 1.92-1.83 (m, 2H); 1.78-1.71 (m, 2H).
APCI-MS: *m/z* 208(MH⁺).

5 **Intermediate Compound: 5-Chloro-3*H*-spiro[1-benzofuran-2,3'-pyrrolidine]**

Step I:

1-Benzyl-3-(5-chloro-2-fluorobenzyl)pyrrolidin-3-ol

To a stirring suspension of magnesium strip (1.39 g, 57.06 mmol) in diethyl ether (10 mL)
10 was added a crystal iodine followed by 0.5 mL of 2-(bromomethyl)-4-chloro-1-fluorobenzene under nitrogen. The reaction was initiated with a high intensity heat gun, then a solution of 2-(bromomethyl)-4-chloro-1-fluorobenzene (12.75 g, 57.06 mmol) in diethyl ether was added at such a speed that gentle reflux was maintained. After addition was complete the reaction mixture was kept on stirring at reflux for 3.5 h, cooled to room
15 temperature and a solution of 1-benzylpyrrolidin-3-one (10.0 g, 57.06 mmol) in diethyl ether (20 mL) was added dropwise with vigorous stirring. After addition was complete the reaction mixture was left overnight at room temperature. This reaction mixture was treated with aqueous ammonium chloride (NH₄Cl) solution and extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulphate (Na₂SO₄), filtered,
20 concentrated and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% ammonium hydroxide, NH₄OH) to give the subtitled compound (650 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 7.39-7.23 (m, 6H); 7.21-7.15 (m, 1H); 6.98 (t, *J* = 9.0 Hz, 1H); 3.68 (d, *J* = 13.0 Hz, 1H); 3.63 (d, *J* = 13.0 Hz, 1H); 3.01-2.89 (m, 3H); 2.65 (d, *J* =
25 9.5 Hz, 1H); 2.42-2.34 (m, 2H); 2.07-1.98 (m, 1H); 1.88-1.75 (m, 1H); 1.64 (br.s, 1H).
APCI-MS: *m/z* 320(MH⁺).

Step II:

1'-Benzyl-5-chloro-3*H*-spiro[1-benzofuran-2,3'-pyrrolidine]

To a suspension of sodium hydride (NaH) (55%, 612 mg, 14.0 mmol) in toluene (10 mL) was added a solution of 1-benzyl-3-(5-chloro-2-fluorobenzyl)pyrrolidin-3-ol (1.3 g, 4.06 mmol) in toluene (20 mL) and the reaction mixture was kept on stirring at reflux, after 5 minutes dimethylformamide (10 mL) was added and the reaction mixture was refluxed for 90 minutes, cooled to room temperature, water (20 mL) was added and extracted with ethyl acetate. The organic layer was dried over sodium sulphate (Na₂SO₄), filtered, concentrated and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% ammonium hydroxide, NH₄OH) to give the subtitled compound (560 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.39-7.24 (m, 5H); 7.10 (s, 1H); 7.06 (dd, *J* = 2.3, 8.5 Hz, 1H); 6.68 (d, *J* = 8.4 Hz, 1H); 3.73 (d, *J* = 13.0 Hz, 1H); 3.70 (d, *J* = 13.0 Hz, 1H); 3.24 (d, *J* = 16.0 Hz, 1H); 3.20 (d, *J* = 16.0 Hz, 1H); 2.99 (d, *J* = 10.4 Hz, 1H); 2.95-2.88 (m, 1H); 2.74-2.64 (m, 2H); 2.43-2.34 (m, 1H); 2.11-2.02 (m, 1H).

APCI-MS: *m/z* 300(MH⁺).

Step III:

5-Chloro-3*H*-spiro[1-benzofuran-2,3'-pyrrolidine]

The experimental procedure is the same as described above for the corresponding piperidine derivative using 1'-benzyl-5-chloro-3*H*-spiro[1-benzofuran-2,3'-pyrrolidine] (555 mg, 1.85 mmol), ethyl chloroformate (261 mg, 2.4 mmol), toluene (5 mL), potassium hydroxide (KOH) (3.0 g), water (3 mL) and ethanol (6 mL) to give the titled compound (240 mg) after silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% ammonium hydroxide, NH₄OH).

¹H-NMR (CDCl₃, 400 MHz): δ 7.13 (s, 1H); 7.08 (dd, *J* = 2.3, 8.5 Hz, 1H); 6.65 (d, *J* = 8.5 Hz, 1H); 3.32-3.16 (m, 4H); 3.07 (ddd, *J* = 4.8, 9.1, 11.2 Hz, 1H); 2.80 (d, *J* = 12.3 Hz, 1H); 2.33-2.24 (m, 1H); 1.93 (ddd, *J* = 7.3, 9.1, 13.7 Hz, 1H).

APCI-MS: *m/z* 210(MH⁺).

Example 34

***N*-(2-{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)acetamide**

A mixture of 5-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidin] (29.3 mg, 0.131 mmol) and
4-(acetylamino)-3-[(2*S*)-oxiran-2-ylmethoxy]phenyl acetate (35 mg, 0.131 mmol) in
ethanol (1.5 mL) was kept on stirring at 80 °C overnight. The volatiles were removed in
vacuo and the residue was purified by HPLC (acetonitrile (CH₃CN) 10-55% in water, 0.1%
trifluoroacetic acid, CF₃COOH) to give the titled compound (35 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.36 (m, 3H); 7.21 (d, *J* = 8.7 Hz, 1H); 6.50 (d, *J* = 2.4
Hz, 1H); 6.40 (dd, *J* = 2.4, 8.7 Hz, 1H); 5.10 (s, 2H); 4.48 (m, 1H); 4.05 (d, *J* = 4.6 Hz,
2H); 3.78-3.63 (m, 2H); 3.56-3.35 (m, 4H); 2.40-2.21 (m, 2H); 2.13 (s, 3H); 2.08-1.95 (m,
2H).

APCI-MS: *m/z* 447(MH⁺).

Example 35

***N*-(2-{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide**

A mixture of 5-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidin] (35 mg, 0.156 mmol) and *N*-
{2-[(2*S*)-oxiran-2-ylmethoxy]phenyl}acetamide (32.3 mg, 0.156 mmol) in ethanol (1.5
mL) was kept on stirring at 80 °C overnight. The volatiles were removed in vacuo and the
residue was purified by silica gel flash chromatography (0-1% methanol in
dichloromethane, 0.1% ammonium hydroxide, NH₄OH) to give the titled compound (45
mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.99 (dd, *J* = 1.3, 7.9 Hz, 1H); 7.29-7.25 (m, 2H); 7.18 (d,
J = 7.8 Hz, 1H); 7.12-7.01 (m, 2H); 6.96-6.91 (m, 1H); 5.00 (s, 2H); 4.25 (m, 1H); 4.13
(dd, *J* = 3.2, 9.9 Hz, 1H); 3.99 (dd, *J* = 6.4, 9.9 Hz, 1H); 3.00-2.89 (m, 2H); 2.67-2.50 (m,
4H); 2.20 (s, 3H); 2.08-1.96 (m, 2H); 1.73 (m, 2H).

APCI-MS: *m/z* 431(MH⁺).

Example 36

2-{{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-methylbenzamide

5 Step I:

2-{{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide

A mixture of 5-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (26 mg, 0.116 mmol) and 4-
10 [(4-methoxybenzyl)oxy]-*N*-methyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide (40 mg, 0.116 mmol) in ethanol (2 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.1% ammonium hydroxide, NH₄OH) to give the subtitled compound (50 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 78.18 (d, *J* = 8.8 Hz, 1H); 8.14 (m, 1H); 7.37 (d, *J* = 8.7
15 Hz, 2H); 7.28 (m, 2H); 7.22 (s, 1H); 7.09 (d, *J* = 8.0 Hz, 1H); 6.97-6.92 (m, 2H); 6.71 (dd, *J* = 2.3, 8.8 Hz, 1H); 6.52 (d, *J* = 2.3 Hz, 1H); 5.08 (s, 2H); 5.05 (s, 2H); 4.25-4.15 (m, 2H); 3.85 (s, 3H); 3.00 (m, 4H); 2.88-2.75 (m, 2H); 2.66-2.46 (m, 3H); 2.06-1.90 (m, 2H); 1.82 (d, *J* = 12.9 Hz, 2H).

APCI-MS: *m/z* 567(MH⁺).

20

Step II:

2-{{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-methylbenzamide

2-{{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-
25 hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide (45 mg, 0.079 mmol) was treated with 10% trifluoroacetic acid (CF₃COOH) in dichloromethane (CH₂Cl₂) (3 mL) for 25 min at room temperature. The volatiles were removed in vacuo and the residue was purified by HPLC (10-45% acetonitrile (CH₃CN) in water, 0.1% ammonium hydroxide, NH₄OH) to give the titled compound (17 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.82 (d, *J* = 8.7 Hz, 1H); 7.30-7.25 (m, 2H); 7.18 (d, *J* = 7.9 Hz, 1H); 6.55 (d, *J* = 2.2 Hz, 1H); 6.48 (dd, *J* = 2.2, 8.7 Hz, 1H); 5.05 (s, 2H); 4.26-4.19 (m, 2H); 4.09-4.04 (m, 1H); 2.98-2.87 (m, 5H); 2.64-2.50 (m, 4H); 2.09-1.97 (m, 2H); 1.73 (d, *J* = 13.2 Hz, 2H).

5 APCI-MS: *m/z* 447(MH⁺).

Example 37

2-**{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxy-2-methoxypropyl]oxy}**-*N*-cyclopropyl-4-hydroxybenzamide

10

Step I:

2-**{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}**-*N*-cyclopropyl-4-**[(4-methoxybenzyl)oxy]**benzamide

15

A mixture of 5-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (40 mg, 0.178 mmol) and *N*-cyclopropyl-4-**[(4-methoxybenzyl)oxy]**-2-**{[(2*S*)-2-methyloxiran-2-yl]methoxy}**benzamide (68 mg, 0.178 mmol) in ethanol (2 mL) was stirred at 80 °C for 6h. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-0.9% methanol in dichloromethane, 0.1% ammonium hydroxide, NH₄OH) to give the subtitled compound (45 mg).

20

¹H-NMR (CDCl₃), 400 MHz): δ 8.21 (br.s, 1H); 7.99 (d, *J* = 8.7 Hz, 1H); 7.36 (d, *J* = 8.7 Hz, 2H); 7.27 (m, 1H); 7.20 (s, 1H); 7.03 (d, *J* = 8.0 Hz, 1H); 6.92 (m, 2H); 6.70 (dd, *J* = 2.3, 8.8 Hz, 1H); 6.50 (d, *J* = 2.3 Hz, 1H); 5.03 (s, 2H); 5.01 (s, 2H); 3.86 (s, 2H); 2.85 (s, 3H); 3.05 (m, 1H); 2.91-2.80 (m, 3H); 2.75 (m, 1H); 2.67 (d, *J* = 13.9 Hz, 1H); 2.50 (d, *J* = 13.9 Hz, 1H); 1.95 (m, 2H); 1.75 (m, 2H); 1.30 (s, 3H); 0.83 (m, 2H); 0.62 (m, 2H).

25

APCI-MS: *m/z* 607(MH⁺).

Step II:

2-**{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxy-2-methoxypropyl]oxy}**-*N*-cyclopropyl-4-hydroxybenzamide

2-[[[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy]-*N*-cyclopropyl-4-[(4-methoxybenzyl)oxy]benzamide (40 mg, 0.065 mmol) was treated with 10% trifluoroacetic acid (CF₃COOH) (3 mL) for 25 min at room temperature. The volatiles were removed in vacuo and the residue was purified by HPLC
5 (10-55% acetonitrile (CH₃CN) in water, 0.1% ammonium hydroxide, NH₄OH) to give the titled compound (30 mg).

¹H-NMR (CD₃OD), 400 MHz): δ 7.84 (d, *J* = 8.4 Hz, 1H); 7.25 (m, 2H); 7.16 (d, *J* = 7.6 Hz, 1H); 6.45 (m, 2H); 5.00 (s, 2H); 4.11 (d, *J* = 9.0 Hz, 1H); 3.93 (d, *J* = 9.0 Hz, 1H); 2.93 (m, 1H); 2.88 (m, 2H); 2.74-2.49 (m, 4H); 1.99 (m, 2H); 1.62 (m, 2H); 1.31 (s, 3H);
10 0.79 (m, 2H); 0.65 (m, 2H).

APCI-MS: *m/z* 487(MH⁺).

Example 38

2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-
15 hydroxypropyl]oxy]-4-hydroxy-*N*-(2-hydroxyethyl)benzamide

Step I:

Methyl-4-[(4-methoxybenzyl)oxy]-2-[(2S)-oxiran-2-ylmethoxy]benzoate

A mixture of 2(S)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (518 mg, 2.0 mmol), methyl
20 2-hydroxy-4-[(4-methoxybenzyl)oxy]benzoate (576.6 mg, 2.0 mmol) and cesium carbonate (Cs₂CO₃) (812.5 mg, 2.5 mmol) in dimethylformamide (10 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate, Na₂SO₄, filtered, concentrated in vacuo and the residue was purified by silica gel flash chromatography (0-
25 30% ethyl acetate in petroleum ether) to give the subtitled compound (600 mg).

¹H-NMR (CDCl₃), 400 MHz): δ 7.87 (d, *J* = 8.7 Hz, 1H); 7.39-7.34 (m, 2H); 6.97-6.92 (m, 2H); 6.61 (dd, *J* = 2.4, 8.7 Hz, 1H); 6.59 (d, *J* = 2.2 Hz, 1H); 5.04 (s, 2H); 4.31 (dd, *J* = 2.9, 11.1 Hz, 1H); 4.07 (dd, *J* = 4.8, 11.1 Hz, 1H); 3.88 (s, 3H); 3.85 (s, 3H); 3.40 (m, 1H); 2.92 (m, 2H).

30 APCI-MS: *m/z* 345(MH⁺).

Step II:**Methyl 2-([(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-[(4-methoxybenzyl)oxy]benzoate**

5 A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (150 mg, 0.67 mmol) and methyl-4-[(4-methoxybenzyl)oxy]-2-[(2*S*)-oxiran-2-ylmethoxy]benzoate (230.5 mg, 0.67 mmol) in ethanol (3 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane) to give the subtitled compound (370 mg).

10 ¹H-NMR (CDCl₃), 400 MHz): δ 7.87 (d, *J* = 8.8 Hz, 1H); 7.40-7.35 (m, 2H); 7.12 (m, 1H); 7.07 (dd, *J* = 2.2, 8.4 Hz, 1H); 6.98-6.93 (m, 2H); 6.69 (d, *J* = 8.4 Hz, 1H); 6.63 (d, *J* = 2.2 Hz, 1H); 6.60 (s, 1H); 5.06 (s, 2H); 4.19 (m, 2H); 4.03 (m, 1H); 3.89 (s, 3H); 3.85 (s, 3H); 3.00 (s, 2H); 2.80 (m, 1H); 2.73-2.58 (m, 5H); 2.00 (m, 2H); 1.82 (m, 2H).

APCI-MS: *m/z* 568(MH⁺).

15

Step III:**2-([(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-*N*-(2-hydroxyethyl)-4-[(4-methoxybenzyl)oxy]benzamide**

20 A mixture of methyl 2-([(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-[(4-methoxybenzyl)oxy]benzoate (60 mg, 0.105 mmol) and 2-aminoethanol (0.256 mL, 4.2 mmol) in methanol (2 mL) was refluxed for 72h. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% ammonium hydroxide, NH₄OH) to give the subtitled compound (30 mg).

25 ¹H-NMR (CDCl₃), 400 MHz): δ 8.49 (t, *J* = 5.4 Hz, 1H); 8.17 (d, *J* = 8.8 Hz, 1H); 7.40-7.35 (m, 2H); 7.12 (s, 1H); 7.09 (dd, *J* = 2.2, 8.4 Hz, 1H); 6.98-6.93 (m, 2H); 6.72 (dd, *J* = 2.2, 8.8 Hz, 1H); 6.69 (d, *J* = 8.5 Hz, 1H); 6.55 (d, *J* = 2.2 Hz, 1H); 5.06 (s, 2H); 4.21 (m, 2H); 3.94 (dd, *J* = 7.2, 10.1 Hz, 1H); 3.85 (s, 3H); 3.83 (d, *J* = 4.8 Hz, 2H); 3.70 (m, 1H); 3.60 (m, 1H); 3.00 (s, 2H); 2.91-2.76 (m, 2H); 2.68-2.53 (m, 4H); 2.00 (m, 2H); 1.80 (m, 30 2H).

APCI-MS: m/z 597(MH^+).

Step IV:

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-(2-hydroxyethyl)benzamide

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-(2-hydroxyethyl)-4-[(4-methoxybenzyl)oxy]benzamide (27 mg, 0.045 mmol) was treated with 10% trifluoroacetic acid (CF_3COOH) in dichloromethane (CH_2Cl_2) (3 mL) for 30 min at room temperature. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-4% methanol in dichloromethane, 0.2% ammonium hydroxide, NH_4OH) to give the titled compound (16 mg).

1H -NMR (CD_3OD), 400 MHz): δ 7.85 (d, J = 8.6 Hz, 1H); 7.13 (m, 1H); 7.19 (dd, J = 2.4, 8.5 Hz, 1H); 6.65 (d, J = 8.5 Hz, 1H); 6.52 (d, J = 2.2 Hz, 1H); 6.49 (dd, J = 2.2, 8.6 Hz, 1H); 4.27-4.17 (m, 2H); 4.06 (dd, J = 5.9, 9.4 Hz, 1H); 3.73 (t, J = 5.6 Hz, 2H); 3.53 (m, 2H); 3.00 (s, 2H); 2.70 (m, 4H); 2.62 (d, J = 6.4 Hz, 2H); 1.95 (m, 2H); 1.84 (m, 2H).

APCI-MS: m/z 477(MH^+).

Example 39

***N*-(2-Aminoethyl)-2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzamide**

Step I:

***N*-(2-Aminoethyl)-2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzamide**

A mixture of 2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoic acid (50 mg, 0.084 mmol) and *N,N*-carbonyldiimidazole (14 mg, 0.084 mmol) in dimethylformamide (3 mL) was kept on stirring at room temperature for 1h. Then ethylenediamine (11 mg, 0.168 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction

mixture was partitioned between ethyl acetate and water, the organic layer was dried over sodium sulphate, Na₂SO₄, filtered, concentrated in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% ammonium hydroxide, NH₄OH) to give the subtitled compound (22 mg).

¹H-NMR (CD₃OD), 400 MHz): δ 7.93 (d, *J* = 8.9 Hz, 1H); 7.45 (m, 2H); 7.12 (s, 1H); 7.04 (dd, *J* = 2.3, 8.6 Hz, 1H); 6.95-6.90 (m, 2H); 6.73 (s, 1H); 6.70 (d, *J* = 2.2 Hz, 1H); 6.64 (d, *J* = 8.5 Hz, 1H); 5.08 (s, 2H); 4.27 (dd, *J* = 2.7, 9.7 Hz, 1H); 4.23-4.15 (m, 1H); 4.05 (dd, *J* = 6.6, 9.8 Hz, 1H); 3.80 (s, 3H); 3.48 (t, *J* = 5.9 Hz, 2H); 2.96 (s, 2H); 2.86 (t, *J* = 6.1 Hz, 2H); 2.68 (m, 4H); 2.56 (d, *J* = 6.4 Hz, 2H); 1.90 (m, 2H); 1.80 (m, 2H).

APCI-MS: *m/z* 596(MH⁺).

Step II:

N-(2-Aminoethyl)-2-[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzamide

N-(2-Aminoethyl)-2-[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzamide ((22mg, 0.037 mmol) was treated with 10% trifluoroacetic acid (CF₃COOH) in dichloromethane (2 mL) for 20 min at room temperature. The volatiles were removed in vacuo and the residue was purified by HPLC (10-60% acetonitrile (CH₃CN) in water, 0.1% ammonium hydroxide, NH₄OH) to give the titled compound (8 mg).

¹H-NMR (CD₃OD), 400 MHz): δ 7.83 (d, *J* = 8.6 Hz, 1H); 7.14 (m, 1H); 7.04 (dd, *J* = 2.2, 8.4 Hz, 1H); 6.65 (d, *J* = 8.4 Hz, 1H); 6.50 (d, *J* = 2.1 Hz, 1H); 6.47 (dd, *J* = 2.2, 8.6 Hz, 1H); 4.27-4.19 (m, 2H); 4.04 (m, 1H); 3.50 (t, *J* = 6.0 Hz, 2H); 3.02 (s, 2H); 2.90 (t, *J* = 6.0 Hz, 2H); 2.69 (m, 4H); 2.60 (d, *J* = 6.2 Hz, 2H); 1.94 (m, 2H); 1.84 (m, 2H).

APCI-MS: *m/z* 476(MH⁺).

Example 40

2-[(2*S*)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-methylbenzamide

Step I:**2-[[[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide**

A mixture of 5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (20 mg, 0.096 mmol) and 4-
5 [(4-methoxybenzyl)oxy]-*N*-methyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide (34.3 mg,
0.099 mmol) in ethanol (2 mL) was stirred at 80 °C overnight. The volatiles were removed
in vacuo and the residue was purified by silica gel flash chromatography (0-0.8% methanol
in dichloromethane, 0.1% ammonium hydroxide, NH₄OH) to give the subtitled compound
(36 mg).

10 ¹H-NMR (CDCl₃), 400 MHz): δ 8.16 (d, *J* = 8.7 Hz, 1H); 8.10 (m, 1H); 7.36 (m, 2H);
6.96-6.91 (m, 2H); 6.89-6.77 (m, 2H); 7.72-6.64 (m, 2H); 6.54 (d, *J* = 2.3 Hz, 1H); 5.00 (s,
2H); 4.20-4.10 (m, 2H); 3.96 (dd, *J* = 5.4, 9.4 Hz, 1H); 3.83 (s, 3H); 3.01 (s, 3H); 3.00 (s,
2H); 2.90 (m, 1H); 2.80 (m, 1H); 2.64-2.50 (m, 4H); 2.00 (m, 2H); 1.83 (m, 2H).
APCI-MS: *m/z* 551(MH⁺).

Step II:**2-[[[(2S)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-hydroxy-*N*-methylbenzamide****2-[[[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-**

20 hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide (32 mg, 0.058
mmol) was treated with 10% trifluoroacetic acid (CF₃COOH) in dichloromethane (2.5 mL)
for 20 min at room temperature. The volatiles were removed in vacuo and the residue was
purified by HPLC (10-50% acetonitrile (CH₃CN) in water, 0.1% ammonium hydroxide,
NH₄OH) to give the titled compound (11 mg).

25 ¹H-NMR (CDCl₃), 400 MHz): δ 7.82 (d, *J* = 8.6 Hz, 1H); 6.50 (dd, *J* = 2.7, 8.1 Hz, 1H);
6.81-6.74 (m, 1H); 6.62 (dd, *J* = 4.2, 8.7 Hz, 1H); 6.52 (d, *J* = 2.2 Hz, 1H); 6.48 (dd, *J* =
2.2, 8.6 Hz, 1H); 4.24-4.17 (m, 2H); 4.08-4.02 (m, 1H); 3.01 (s, 2H); 2.92 (s, 3H); 2.77-
2.63 (m, 4H); 2.60 (d, *J* = 6.2 Hz, 2H); 1.94 (m, 2H); 1.84 (m, 2H).

APCI-MS: *m/z* 431(MH⁺).

Example 41

***N*-(2-([(2*S*)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-hydroxyphenyl)acetamide**

- 5 A mixture of 5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (20 mg, 0.096 mmol) and 4-(acetylamino)-3-[(2*S*)-oxiran-2-ylmethoxy]phenyl acetate (25.5 mg, 0.096 mmol) in ethanol (2 mL) was kept on stirring at 80 °C over the weekend. The volatiles were removed in vacuo and the residue was purified by HPLC (10-35% acetonitrile (CH₃CN) in water, 0.1% ammonium hydroxide, NH₄OH) to give the titled compound (14 mg).
- 10 ¹H-NMR (CD₃OD), 400 MHz): δ 7.57 (d, *J* = 8.7 Hz, 1H); 6.90 (m, 1H); 6.81-6.74 (m, 1H); 6.63 (dd, *J* = 4.2, 8.7 Hz, 1H); 6.48 (d, *J* = 2.5 Hz, 1H); 6.36 (dd, *J* = 2.6, 8.7 Hz, 1H); 4.18 (m, 1H); 4.05 (dd, *J* = 3.4, 9.8 Hz, 1H); 3.93 (dd, *J* = 6.2, 9.8 Hz, 1H); 3.01 (s, 2H); 2.70 (m, 4H); 2.61 (t, *J* = 7.0 Hz, 2H); 2.14 (s, 3H); 1.96 (m, 2H); 1.85 (m, 2H).
- APCI-MS: *m/z* 431(MH⁺).

15

Example 42

***N*-(2-([(2*S*)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)phenyl)acetamide**

- A mixture of 5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (8 mg, 0.038 mmol) and *N*-{2-[(2*S*)-oxiran-2-ylmethoxy]phenyl}acetamide (8 mg, 0.038 mmol) in ethanol (1.5 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by HPLC (10-70% acetonitrile (CH₃CN) in water, 0.1% ammonium hydroxide, NH₄OH) to give the titled compound (11 mg).
- 20 ¹H-NMR (CD₃OD), 400 MHz): δ 7.99 (dd, *J* = 1.5, 8.1 Hz, 1H); 7.08 (m, 1H); 7.03 (m, 1H); 6.94 (m, 1H); 6.90 (m, 1H); 6.77 (m, 1H); 6.63 (dd, *J* = 4.2, 8.8 Hz, 1H); 4.19 (m, 1H); 4.12 (dd, *J* = 3.2, 9.9 Hz, 1H); 3.98 (dd, *J* = 6.4, 9.9 Hz, 1H); 3.05 (s, 2H); 2.70 (m, 4H); 2.62 (m, 2H); 2.19 (s, 3H); 1.94 (m, 2H); 1.85 (m, 2H).
- APCI-MS: *m/z* 415(MH⁺).

30 **Example 43**

***N*-[2-({(2*S*)-3[(2*S*)-5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)phenyl]acetamide**

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,3'-pyrrolidine] (34.5 mg, 0.167 mmol) and
5 *N*-{2-[(2*S*)-oxiran-2-ylmethoxy]phenyl}acetamide (35 mg, 0.167 mmol) in ethanol (1.5 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1% methanol (CH₃OH) in dichloromethane (CH₂Cl₂), 0.2% ammonium hydroxide, NH₄OH) to give a mixture of two isomers (55 mg). This mixture was subjected to chiral HPLC to give the titled compound
10 (17 mg) and other isomer (14 mg).

¹H-NMR (CD₃OD), 400 MHz): δ 7.99 (dd, *J* = 1.4, 8.0 Hz, 1H); 7.15 (m, 1H); 7.11-7.01 (m, 3H); 6.93 (m, 1H); 6.66 (d, *J* = 8.5 Hz, 1H); 4.18-4.11 (m, 2H); 3.99 (dd, *J* = 7.0, 10.6 Hz, 1H); 3.25 (m, 2H); 3.11 (d, *J* = 10.8 Hz, 1H); 3.00 (m, 1H); 2.86-2.69 (m, 4H); 2.33-2.25 (m, 1H); 2.18 (s, 3H); 2.13-2.05 (m, 1H).

15 APCI-MS: *m/z* 417(MH⁺).

Example 44

***N*-[2-({(2*S*)-3[(2*R*)-5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)phenyl]acetamide**

20 ¹H-NMR (CD₃OD), 400 MHz): δ 7.99 (dd, *J* = 1.4, 8.0 Hz, 1H); 7.15 (m, 1H); 7.11-7.01 (m, 3H); 6.93 (m, 1H); 6.66 (d, *J* = 8.5 Hz, 1H); 4.18-4.11 (m, 2H); 3.99 (dd, *J* = 7.0, 10.6 Hz, 1H); 3.25 (m, 2H); 3.11 (d, *J* = 10.8 Hz, 1H); 3.00 (m, 1H); 2.86-2.69 (m, 4H); 2.33-2.25 (m, 1H); 2.18 (s, 3H); 2.13-2.05 (m, 1H).

25 APCI-MS: *m/z* 417(MH⁺).

Example 45

***N*-[2-({(2*S*)-3-[(2*S*)-5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)-4-methoxyphenyl]acetamide**

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,3'-pyrrolidine] (60 mg, 0.286 mmol) and *N*-{4-methoxy-2-[(2*S*)-oxiran-2-ylmethoxy]phenyl}acetamide (68 mg, 0.286 mmol) in ethanol (2 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1% methanol (CH₃OH) in dichloromethane (CH₂Cl₂), 0.2% ammonium hydroxide, NH₄OH) to give a mixture of two isomers and this was subjected to chiral HPLC to give the titled compound (35 mg) and the other isomer (35 mg).

¹H-NMR (CD₃OD), 400 MHz): δ 7.73 (d, *J* = 8.8 Hz, 1H); 7.14 (m, 1H); 7.04 (dd, *J* = 2.2, 8.4 Hz, 1H); 6.65 (d, *J* = 8.5 Hz, 1H); 6.60 (d, *J* = 2.5 Hz, 1H); 6.49 (dd, *J* = 2.6, 8.8 Hz, 1H); 4.15-4.06 (m, 2H); 3.96 (dd, *J* = 6.2, 9.8 Hz, 1H); 3.79 (s, 3H); 3.25 (m, 2H); 3.11 (dd, *J* = 10.7, 15.9 Hz, 1H); 2.99 (m, 1H); 2.85-2.64 (m, 4H); 2.25 (m, 1H); 2.13 (s, 3H); 2.08 (m, 1H).

APCI-MS: *m/z* 447(MH⁺).

Example 46

N-[2-({(2*S*)-3-[(2*R*)-5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)-4-methoxyphenyl]acetamide

¹H-NMR (CD₃OD), 400 MHz): δ 7.73 (d, *J* = 8.8 Hz, 1H); 7.14 (m, 1H); 7.04 (dd, *J* = 2.2, 8.4 Hz, 1H); 6.65 (d, *J* = 8.5 Hz, 1H); 6.60 (d, *J* = 2.5 Hz, 1H); 6.49 (dd, *J* = 2.6, 8.8 Hz, 1H); 4.15-4.06 (m, 2H); 3.96 (dd, *J* = 6.2, 9.8 Hz, 1H); 3.79 (s, 3H); 3.25 (m, 2H); 3.11 (dd, *J* = 10.7, 15.9 Hz, 1H); 2.99 (m, 1H); 2.85-2.64 (m, 4H); 2.25 (m, 1H); 2.13 (s, 3H); 2.08 (m, 1H).

APCI-MS: *m/z* 447(MH⁺).

Example 47

2-[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-methylbenzamide

Step I:

2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,3'-pyrrolidine] (80 mg, 0.381 mmol) and
5 4-[(4-methoxybenzyl)oxy]-*N*-methyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide (130.8 mg, 0.381 mmol) in ethanol (3 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.2% ammonium hydroxide, NH₄OH) to give the subtitled compound (165 mg).

¹H-NMR (CDCl₃), 400 MHz): δ 8.15 (d, *J* = 8.8 Hz, 1H); 8.04 (m, 1H); 7.36 (m, 2H); 7.13 (br,s, 1H); 7.09 (m, 1H); 6.93 (m, 2H); 6.72-6.66 (m, 2H); 6.54 (d, *J* = 2.2 Hz, 1H); 5.05 (s, 2H); 4.17 (dd, *J* = 3.2, 9.5 Hz, 1H); 4.09 (m, 1H); 3.98 (dd, *J* = 5.7, 9.5 Hz, 1H); 3.83 (s, 3H); 3.30-2.83 (m, 9H); 2.72 (m, 1H); 2.60 (dd, *J* = 3.4, 12.1 Hz, 1H); 2.34 (m, 2H); 2.08 (m, 2H).

15 APCI-MS: *m/z* 553(MH⁺).

Step II:

2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl)-2-hydroxypropyl]oxy]-4-hydroxy-*N*-methylbenzamide

20 2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide (160 mg, 0.289 mmol) was treated with 10% trifluoroacetic acid (CF₃COOH) in dichloromethane (CH₂Cl₂) for 25 min at room temperature. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol (CH₃OH) in dichloromethane
25 (CH₂Cl₂), 0.2% ammonium hydroxide, NH₄OH) to give the titled compound (80 mg).
APCI-MS: *m/z* 433(MH⁺).

Example 48

2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-hydroxybenzoic acid (trifluoroacetate)

Step I:**2-{{{(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-[(4-methoxybenzyl)benzoic acid**

5 To a solution of methyl 2-{{{(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-[(4-methoxybenzyl)oxy]benzoate (150 mg, 0.264 mmol) in ethanol (2 mL) was added aqueous solution of potassium hydroxide (KOH) (770 mg, KOH in 0.77 mL water) and the reaction mixture was stirred at reflux overnight, cooled to 0 °C and the pH was adjusted to 2.0 by addition of aqueous hydrochloric acid (HCl). The
10 whole was extracted with ethyl acetate. The organic layer was dried over sodium sulphate, Na₂SO₄, filtered and concentrated to give the subtitled compound (145 mg).
¹H-NMR (CD₃OD), 400 MHz): δ 7.78 (d, *J* = 8.4 Hz, 1H); 7.35 (m, 2H); 7.19 (m, 1H); 7.09 (dd, *J* = 2.2, 8.4 Hz, 1H); 6.93 (m, 2H); 6.75-6.65 (m, 3H); 5.09 (s, 2H); 4.40 (m, 1H); 4.24 (dd, *J* = 4.0, 9.3 Hz, 1H); 4.06 (dd, *J* = 5.5, 9.3 Hz, 1H); 3.80 (s, 3H); 3.70-3.53 (m,
15 2H); 3.51-3.35 (m, 4H); 3.14 (s, 2H); 2.33 (m, 2H); 2.12 (d, *J* = 14.8 Hz, 2H).
APCI-MS: *m/z* 554(MH⁺).

Step II:

20 **2-{{{(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoic acid (trifluoroacetate)**
2-{{{(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-[(4-methoxybenzyl)benzoic acid (31 mg, 0.052 mmol) was treated with 10% trifluoroacetic acid (CF₃COOH) in dichloromethane (CH₂Cl₂) (2 mL) at room temperature for 20 min. The volatiles were removed in vacuo and the residue was purified
25 by HPLC (10-55% acetonitrile (CH₃CN) in water, 0.1% trifluoroacetic acid (CF₃COOH)) to give the titled compound (15 mg).
APCI-MS: *m/z* 434(MH⁺).

Example 49

3(S)-1-(2-{{{(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)pyrrolidin-3-ol

Step I:

5 (3S)-1-{2-{{{(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-[(4-methoxybenzyl)oxy]benzoyl}pyrrolidin-3-ol

A mixture of 2-{{{(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoic acid (100 mg, 0.169 mmol) and *N,N*-

carbonyldiimidazole (30 mg, 0.186 mmol) in dimethylformamide (3mL) was stirred at

10 room temperature for 1h. Then (3S)-pyrrolidin-3-ol (76.3 mg, 0.845 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water, the organic layer was dried over sodium

sulphate, Na₂SO₄, filtered, concentrated in vacuo and the residue was purified by silica gel flash chromatography (0-2.5% methanol in dichloromethane, 0.2% ammonium hydroxide,

15 NH₄OH) to give the subtitled compound (55 mg).

APCI-MS: m/z 623(MH⁺).

Step II:

3(S)-1-(2-{{{(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)pyrrolidin-3-ol

20 (3S)-1-{2-{{{(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-[(4-methoxybenzyl)oxy]benzoyl}pyrrolidin-3-ol (50 mg, 0.08 mmol) was treated with 10% trifluoroacetic acid (CF₃COOH) in dichloromethane (CH₂Cl₂)

(3 mL) at room temperature for 20 min. The volatiles were removed in vacuo and the

25 residue was purified by silica gel flash chromatography (0-4.5% methanol (CH₃OH) in dichloromethane (CH₂Cl₂), 0.2% ammonium hydroxide, NH₄OH) to give the titled compound (25 mg).

¹H-NMR (CD₃OD), 400 MHz): δ 7.13 (m, 1H); 7.08 (dd, *J* = 2.5, 8.2 Hz, 1H); 7.03 (dd, *J* = 2.3, 8.5 Hz, 1H); 6.65 (d, *J* = 8.4 Hz, 1H); 6.49 (m, 1H); 6.44 (m, 1H); 4.48 (m, 0.5 H);

4.35 (m, 0.5H); 4.10 (m, 1H); 4.03 (m, 1H); 3.96 (dd, $J = 5.6, 9.7$ Hz, 1H); 3.67 (m, 1H); 3.62-3.50 (m, 2H); 3.30 (m, 1H); 3.00 (s, 2H); 2.78-2.52 (m, 6H); 2.12-1.77 (m, 6H).
APCI-MS: m/z 503(MH^+).

5 **Example 50**

3(R)-1-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)pyrrolidin-3-ol

Step I:

10 **(3R)-1-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoyl)pyrrolidin-3-ol**

A mixture of 2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoic acid (60 mg, 0.101 mmol) and *N,N*-carbonyldiimidazole (17.5 mg, 0.108 mmol) in dimethylformamide (3mL) was stirred at
15 room temperature for 1h. Then (3R)-pyrrolidin-3-ol (47 mg, 0.540 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water, the organic layer was dried over sodium sulphate, Na_2SO_4 , filtered, concentrated in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% ammonium hydroxide,
20 NH_4OH) to give the subtitled compound (64 mg).
APCI-MS: m/z 623(MH^+).

Step II:

25 **3(R)-1-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)pyrrolidin-3-ol**

(3R)-1-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoyl)pyrrolidin-3-ol (60mg, 0.096 mmol) was treated with 10% trifluoroacetic acid (CF_3COOH) in dichloromethane (CH_2Cl_2) (3 mL) at room temperature for 20 min. The volatiles were removed in vacuo and the
30 residue was purified by silica gel flash chromatography (0-5% methanol (CH_3OH) in

dichloromethane (CH₂Cl₂), 0.2% ammonium hydroxide, NH₄OH) to give the titled compound (8 mg).

¹H-NMR (CD₃OD), 400 MHz): δ 7.13 (m, 1H); 7.08 (dd, *J* = 2.5, 8.2 Hz, 1H); 7.03 (dd, *J* = 2.3, 8.5 Hz, 1H); 6.65 (d, *J* = 8.4 Hz, 1H); 6.49 (m, 1H); 6.44 (m, 1H); 4.48 (m, 0.5 H); 4.35 (m, 0.5H); 4.10 (m, 1H); 4.03 (m, 1H); 3.96 (dd, *J* = 5.6, 9.7 Hz, 1H); 3.67 (m, 1H); 3.62-3.50 (m, 2H); 3.30 (m, 1H); 3.00 (s, 2H); 2.78-2.52 (m, 6H); 2.12-1.77 (m, 6H).
APCI-MS: *m/z* 503(MH⁺).

Example 51

3-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-(morpholin-4-ylcarbonyl)phenol

Step I:

(2S)-1-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-[5-[(4-methoxybenzyl)oxy]-2-(morpholin-4-ylcarbonyl)phenoxy]propan-2-ol

A mixture of 2-[[[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-hydroxybenzoic acid (100 mg, 0.169 mmol) and *N,N*-carbonyldiimidazole (35 mg, 0.215 mmol) in dimethylformamide (3mL) was stirred at room temperature for 1h. Then morpholine (250 mg, 2.86 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water, the organic layer was dried over sodium sulphate, Na₂SO₄, filtered, concentrated in vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% ammonium hydroxide, NH₄OH) to give the subtitled compound (58 mg).

APCI-MS: *m/z* 623 (MH⁺).

Step II:

3-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-(morpholin-4-ylcarbonyl)phenol

(2S)-1-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-[5-[(4-methoxybenzyl)oxy]-2-(morpholin-4-ylcarbonyl)phenoxy]propan-2-ol (55 mg, 0.088 mmol) was treated with 10% trifluoroacetic acid (CF₃COOH) in dichloromethane (CH₂Cl₂) (3 mL) for 25 min at room temperature. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol (CH₃OH) in dichloromethane (CH₂Cl₂), 0.2% ammonium hydroxide, NH₄OH) to give the titled compound (24 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.13 (m, 1H); 7.07-7.01 (m, 2H); 6.65 (d, *J* = 8.5 Hz, 1H); 6.50 (d, *J* = 2.1 Hz, 1H); 6.45 (dd, *J* = 2.1, 8.2 Hz, 1H); 4.15-3.92 (m, 3H); 3.87-3.37 (m, 8H); 3.00 (s, 2H); 2.78-2.49 (m, 6H); 1.94 (m, 2H); 1.83 (m, 2H).

APCI-MS: *m/z* 503(MH⁺).

Example 52

2-{[(2S)-3-(5-chloro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-methylbenzamide trifluoroacetate (salt)

Step I:

2-Hydroxy-*N*-methylbenzamide

A solution of methyl salicylate (5.16 mL, 40 mmol) in methanol (10 mL) was added dropwise to aqueous 40% methylamine (18.1 mL, 210 mmol) at 0 °C. After addition was complete the reaction mixture was kept on stirring at room temperature overnight. The volatiles were removed in vacuo to give the subtitled compound (5.48 g).

¹H-NMR (CD₃OD, 400 MHz): δ 7.70 (dd, *J* = 1.5, 7.9 Hz, 1H); 7.38-7.32 (, 2H); 6.90-6.83 (m, 2H); 2.85 (s, 3H).

Step II:

N-Methyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide

A mixture of (2S)-oxiran-2-ylmethyl-3-nitrobenzenesulfonate (388.5 mg, 1.50 mmol), 2-hydroxy-*N*-methylbenzamide (226.5 mg, 1.50 mmol) and cesium carbonate (586 mg, 1.80 mmol) in dimethylformamide (6 mL) was kept on stirring at room

temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was dried over sodium sulphate, Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-50% ethyl acetate in petroleum ether) to give the subtitled compound (284 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 8.39 (m, 1H); 7.90 (br.s, 1H); 7.06-6.98 (m, 2H); 6.95-6.89 (m, 1H); 4.38 (dd, *J* = 2.5, 11.4 Hz, 1H); 3.98 (dd, *J* = 6.0, 11.4 Hz, 1H); 3.40 (m, 1H); 2.97 (t, *J* = 5.0 Hz, 1H); 2.81 (dd, *J* = 2.7, 4.8 Hz, 1H); 2.21 (s, 3H).
APCI-MS: *m/z* 208 (MH⁺).

Step III:

2-{[(2S)-3-(5-chloro-1'H-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-N-methylbenzamide trifluoroacetate (salt)

A mixture of 5-chlorospiro[1,3-benzodioxole-2,4'-piperidine] (22.5 mg, 0.1 mmol) and *N*-methyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide (20.7 mg, 0.1 mmol) in ethanol (2 mL) was kept on stirring at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by preparative HPLC (eluent: [acetonitrile /water + 0.1 % TFA]) to afford the titled compound as a colourless solid (28 mg, 51 %)

¹H-NMR (acetone-d₆, 400 MHz): δ 7.94 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.46 (td, *J* = 7.8, 1.8 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.93 - 6.86 (m, 3H), 4.73 (m, 1H), 4.27 (m, 2H), 3.71 (dd, *J* = 13.4, 2.9 Hz, 2H), 3.58 (dd, *J* = 13.4, 9.5 Hz, 2H), 2.92 (s, 3H), 2.55 (br. s, 4H), 2.08 (m, 2H, covered by the signal of solvent).

APCI-MS: *m/z* 433 (MH⁺).

Example 53

N-(2-{[(2S)-3-(6-chloro-3,4-dihydro-1'H-spiro[chromene-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide trifluoroacetate (salt)

A mixture of 6-chloro-3,4-dihydrospiro[chromene-2,4'-piperidine] (23.8 mg, 0.1 mmol) and *N*-{2-[(2S)-Oxiran-2-ylmethoxy]phenyl}acetamide (20.7 mg, 0.1 mmol) in ethanol (3 mL) was kept on stirring at 80 °C overnight. The volatiles were removed in vacuo and the

residue was purified by preparative HPLC (eluent: [acetonitrile /water + 0.1 % TFA]) to afford the titled compound as a colourless solid (40 mg, 71 %).

¹H-NMR (acetone-d₆, 400 MHz): δ 8.74 (br. s, 1H), 8.29 (d, *J* = 7.5 Hz, 1H), 7.15 (s, 1H), 7.11 (d, *J* = 8.8 Hz, 1H), 6.99 (d, *J* = 3.8 Hz, 2H), 6.97 - 6.85 (m, 2H), 4.54 (m, 1H), 4.11 (m, 2H), 3.81 - 3.43 (m, 6H), 2.88 (t, *J* = 6.8 Hz, 2H), 2.24 - 2.09 (m, 2H), 2.13 (s, 3H), 2.08 (m, 2H, covered by the signal of solvent), 1.95 (t, *J* = 6.8 Hz, 2H)

APCI-MS: *m/z* 445 (MH⁺).

Example 54

N-(2-[[[(2S)-3-(6-chloro-3,4-dihydro-1'H-spiro[chromene-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-fluorophenyl]acetamide trifluoroacetate (salt)

Prepared as described in Example 53 using *N*-{4-fluoro-2-[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide.

¹H-NMR (acetone-d₆, 400 MHz): δ 8.69 (br. s, 1H), 8.24 (m, 1H), 7.15 (s, 1H), 7.11 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.85 (m, 2H), 6.69 (td, *J* = 8.7, 2.8 Hz, 1H), 4.55 (m, 1H), 4.13 (m, 2H), 3.80 - 3.44 (m, 6H), 2.88 (t, *J* = 6.8 Hz, 2H), 2.29 - 2.05 (m, 4H, covered by the signal of solvent), 2.12 (s, 3H), 1.95 (t, *J* = 6.6 Hz, 2H)

APCI-MS: *m/z* 463 (MH⁺).

Example 55

2-[[[(2S)-3-(6-chloro-3,4-dihydro-1'H-spiro[chromene-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-*N*-methylbenzamide trifluoroacetate (salt)

Prepared as described in Example 53 using *N*-methyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide.

¹H-NMR (acetone-d₆, 400 MHz): δ 8.08 (br. s, 1H), 7.96 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.44 (ddd, *J* = 8.3, 7.3, 1.8 Hz, 1H), 7.15 - 7.05 (m, 4H), 6.86 (d, *J* = 8.7 Hz, 1H), 4.70 (m, 1H), 4.24 (m, 2H), 3.77 (m, 2H), 3.60 - 3.45 (m, 4H), 2.91 (d, *J* = 4.4 Hz, 3H), 2.87 (t, *J* = 6.9

Hz, 2H), 2.24 (td, $J = 14.5, 4.3$ Hz, 2H), 2.11- 2.05 (m, 2H, covered by the signal of solvent), 1.92 (m, 2H)

APCI-MS: m/z 445 (MH^+).

5 **Example 56**

N-(2-([(2S)-3-(6-chloro-3,4-dihydro-1'H-spiro[chromene-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-hydroxyphenyl)acetamide trifluoroacetate (salt)

Prepared from 6-chloro-3,4-dihydrospiro[chromene-2,4'-piperidine] as described in

10 **Example 27.**

1H -NMR (acetone- d_6 , 400 MHz): δ 7.92 (d, $J = 8.7$ Hz, 1H), 7.14 (s, 1H), 7.11 (dd, $J = 8.7, 2.5$ Hz, 1H), 6.86 (d, $J = 8.6$ Hz, 1H), 6.52 (d, $J = 2.4$ Hz, 1H), 6.40 (dd, $J = 8.7, 2.5$ Hz, 1H), 4.52 (m, 1H), 4.06 (m, 2H), 3.83 - 3.41 (m, 6H), 2.87 (t, $J = 6.8$ Hz, 2H), 2.27 - 2.08 (m, 4H, covered by the signal of solvent), 2.08 (s, 3H), 1.93 (t, $J = 6.7$ Hz, 2H)

15 APCI-MS: m/z 461 (MH^+).

Example 57

N-(2-([(2S)-3-(6-chloro-3,4-dihydro-1'H-spiro[chromene-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy)-4-hydroxyphenyl)acetamide trifluoroacetate

20

Prepared from 6-chloro-3,4-dihydrospiro[chromene-2,4'-piperidine] as described in

Example 9.

1H -NMR (acetone- d_6 , 400 MHz): δ 7.72 (d, $J = 7.3$ Hz, 1H), 7.11 (m, 2H), 6.86 (d, $J = 8.5$ Hz, 2H), 6.58 (s, 1H), 6.42 (d, $J = 8.7$ Hz, 1H), 3.99 (dd, $J = 22.2, 9.3$ Hz, 2H), 3.91 - 3.46 (m, 6H), 2.85 (t, $J = 6.7$ Hz, 2H), 2.29 (t, $J = 12.6$ Hz, 2H), 2.08 (s, 3H, covered by the signal of solvent), 2.07 (m, 2H, covered by the signal of solvent), 1.90 (s, 28H), 1.50 (s, 3H)

APCI-MS: m/z 475 (MH^+).

30 **Example 58**

***N*-[2-({(2*S*)-3-[(2*R*)-5-chloro-1''*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)-4-hydroxyphenyl]acetamide**

To a cold solution (ice-water bath) of *N*-[2-({(2*S*)-3-[(2*R*)-5-chloro-1''*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)-4-methoxyphenyl]acetamide (30

mg, 0.067 mmol) in CH₂Cl₂ (1.5 mL) was slowly added 1 M solution of BBr₃ in CH₂Cl₂ (0.2 mL). After addition was completed the reaction mixture was stirred at 0 °C for 3h.

After addition of methanol (0.2 mL) the stirring was continued for another 10 min. The volatiles were removed in vacuo and the residue was dissolved in ethyl acetate, washed successively with aqueous NaHCO₃ solution and H₂O. The organic layer was dried over

Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by HPLC (10-60% CH₃CN in H₂O in the presence of 0.1% NH₄OH) to give the titled compound (14 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.57 (d, *J* = 8.7 Hz, 1H); 7.15 (br.s, 1H); 7.05 (dd, *J* = 2.3, 8.6 Hz, 1H); 6.66 (d, *J* = 8.5 Hz, 1H); 6.47 (d, *J* = 2.5 Hz, 1H); 6.36 (dd, *J* = 2.5, 8.7 Hz, 1H); 4.14-4.08 (m, 1H); 4.05 (dd, *J* = 3.5, 9.7 Hz, 1H); 3.92 (dd, *J* = 6.2, 9.7 Hz, 1H); 3.25 (m, 2H); 3.09 (d, *J* = 10.6 Hz, 1H); 3.02 (2.92 (m, 1H); 2.86-2.75 (m, 3H); 2.69 (dd, *J* = 7.3, 12.2 Hz, 1H); 2.32-2.24 (m, 1H); 2.13-2.05 (m, 4H).

APCI-MS: *m/z* 433(MH⁺).

Example 59

***N*-[2-({(2*S*)-3-[(2*S*)-5-chloro-1''*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)-4-hydroxyphenyl]acetamide**

To a cold solution (ice-water bath) of *N*-[2-({(2*S*)-3-[(2*S*)-5-chloro-1''*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)-4-methoxyphenyl]acetamide (30 mg, 0.067 mmol) in CH₂Cl₂ (1.5 mL) was slowly added 1 M solution of BBr₃ in CH₂Cl₂

(0.2 mL). After addition was completed the reaction mixture was stirred at 0 °C for 3h.

After addition of methanol (0.2 mL) the stirring was continued for another 10 min. The volatiles were removed in vacuo and the residue was dissolved in ethyl acetate, washed successively with aqueous NaHCO₃ solution and H₂O. The organic layer was dried over

Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by HPLC (10-60% CH₃CN in H₂O in the presence of 0.1% NH₄OH) to give the titled compound (15 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.57 (d, *J* = 8.7 Hz, 1H); 7.15 (m, 1H); 7.05 (dd, *J* = 2.3, 8.5 Hz, 1H); 6.65 (d, *J* = 8.5 Hz, 1H); 6.47 (d, *J* = 2.5 Hz, 1H); 6.36 (dd, *J* = 2.5, 8.5 Hz, 1H); 4.14-4.07 (m, 1H); 4.04 (dd, *J* = 3.7, 9.9 Hz, 1H); 3.93 (dd, *J* = 6.1, 9.9 Hz, 1H); 3.25 (m, 2H); 3.13 (d, *J* = 10.7 Hz, 1H); 3.03-2.96 (m, 1H); 2.82-2.73 (m, 3H); 3.93 (dd, *J* = 6.1, 9.9 Hz, 1H); 2.32-2.24 (m, 1H); 2.14-2.05 (m, 4H).
APCI-MS: *m/z* 433(MH⁺).

Example 60

3-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-(pyrrolidin-1-ylcarbonyl)phenol

Step I

(2S)-1-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-[5-[(4-methoxybenzyl)oxy]-2-(pyrrolidin-1-ylcarbonyl)phenoxy]propan-2-ol

A mixture of 2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)benzoic acid (hydrochloride) (100 mg, 0.169 mmol) and *N,N*-carbonyldiimidazole (27.5 mg, 0.169 mmol) in DMF (3 mL) was stirred at room temperature for 1h. Then, pyrrolidine (120 mg, 1.69 mmol) in DMF (1 mL) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.2% NH₄OH) to give the subtitled compound (38 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 7.39-7.34 (m, 2H); 7.27-7.20 (m, 1H); 7.13 (m, 1H); 7.05 (dd, *J* = 2.3, 8.5 Hz, 1H); 6.95 (m, 1H); 6.69 (d, *J* = 8.4 Hz, 1H); 6.64-6.59 (m, 2H); 4.13-3.98 (m, 3H); 3.87 (s, 3H); 3.64 (t, *J* = 6.9 Hz, 2H); 3.38 (m, 2H); 3.00 (s, 2H); 2.80 (m, 1H); 2.73-2.49 (m, 5H); 2.03-1.76 (m, 8H).

APCI-MS: *m/z* 607(MH⁺).

Step II

3-([(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-(pyrrolidin-1-ylcarbonyl)phenol

(2S)-1-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-[5-[(4-methoxybenzyl)oxy]-2-(pyrrolidin-1-ylcarbonyl)phenoxy]propan-2-ol (35 mg, 0.057 mmol) was treated with 10% CF₃CO₂H in CH₂Cl₂ (3 mL) at room temperature for 25 min. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (20 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.09 (m, 1H); 7.04-6.97 (m, 2H); 6.61 (d, *J* = 8.5 Hz, 1H); 6.45 (d, *J* = 2.2 Hz, 1H); 6.39 (dd, *J* = 2.0, 8.3 Hz, 1H); 4.09-4.02 (m, 1H); 3.97 (dd, *J* = 4.3, 9.7 Hz, 1H); 3.91 (dd, *J* = 5.7, 9.7 Hz, 1H); 3.51 (t, *J* = 6.8 Hz, 2H); 3.30 (m, 2H); 2.99 (s, 2H); 2.74-2.46 (m, 6H); 1.98-1.74 (m, 8H).

APCI-MS: *m/z* 487(MH⁺).

Example 61

1-(2-([(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-hydroxybenzoyl)piperidin-4-ol

Step I

1-(2-([(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-[(4-methoxybenzyl)oxy]benzoyl)piperidin-4-ol

A mixture of 2-([(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-[(4-methoxybenzyl)benzoic acid (hydrochloride) (100 mg, 0.169 mmol) and *N,N*-carbonyldiimidazole (27.5 mg, 0.169 mmol) in DMF (3 mL) was stirred at room temperature for 1h. Then piperidin-4-ol (20.5 mg, 0.202 mmol) in DMF was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH₄OH) to give the subtitled compound (50 mg).

APCI-MS: *m/z* 637(MH⁺).

Step II

1-(2-{{{(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)piperidin-4-ol

5 1-{2-{{{(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-[(4-methoxybenzyl)oxy]benzoyl}piperidin-4-ol (45 mg, 0.07 mmol) was treated with 10% CF₃CO₂H in CH₂Cl₂ (3 mL) for 25 min at room temperature. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-4.5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled
10 compound (20 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.09 (m, 1H); 7.02-6.92 (m, 2H); 6.60 (d, *J* = 8.5 Hz, 1H); 6.47-6.37 (m, 2H); 4.21-3.78 (m, 4H); 3.58-3.03 (m, 4H); 3.00 (s, 2H); 2.76-2.44 (m, 6H); 1.96-1.22 (m, 8H).

APCI-MS: *m/z* 637(MH⁺).

Example 62

(3S)-1-(2-{{{(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}benzoyl)pyrrolidin-3-ol

A mixture of 2-{{{(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-[(4-methoxybenzyl]benzoic acid (hydrochloride) (60 mg, 0.132
20 mmol) and *N,N*-carbonyldiimidazole (30 mg, 0.184 mmol) in DMF (1.5 mL) was stirred at room temperature for 1h. Then 3(S)-pyrrolidin-3-ol (57.5 mg, 0.66 mmol) in DMF (1 mL) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was
25 dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-2.5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (13 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.45-7.39 (m, 1H); 7.26 (br. d, *J* = 7.2 Hz, 1H); 7.15-7.09 (m, 2H); 7.08-7.01 (m, 2H); 6.65 (d, *J* = 8.5 Hz, 1H); 4.50 (m, 0.5 H); 4.38 (m, 0.5H);

4.17-3.98 (m, 3H); 3.77-3.42 (m, 3H); 3.25 (m, 1H); 3.02 (s, 2H); 2.77-2.52 (m, 6H); 2.14-1.77 (m, 6H).

APCI-MS: m/z 487(MH^+).

5 **Example 63**

3-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-(piperidin-1-ylcarbonyl)phenol

Step I

10 **(2S)-1-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-[5-[(4-methoxybenzyl)oxy]-2-(piperidin-1-ylcarbonyl)phenoxy]propan-2-ol**

A mixture of 2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)benzoic acid (hydrochloride) (100 mg, 0.169 mmol) and *N,N*-carbonyldiimidazole (41 mg, 0.253 mmol) in DMF (1.5 mL) was stirred at
15 room temperature for 1h. Then piperidin (144 mg, 1.79 mmol) in DMF was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.2% NH_4OH) to give the subtitled compound (24 mg).
20 APCI-MS: m/z 621(MH^+).

Step II

3-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-(piperidin-1-ylcarbonyl)phenol

25 **2S)-1-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-[5-[(4-methoxybenzyl)oxy]-2-(piperidin-1-ylcarbonyl)phenoxy]propan-2-ol** (23 mg, 0.037 mmol) was treated with 10% CF_3CO_2H in CH_2Cl_2 (3 mL) at room temperature for 30 min. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2.5% methanol in dichloromethane, 0.2% NH_4OH) to give the titled
30 compound (10 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.13 (m, 1H); 7.03 (dd, *J* = 2.2, 8.5 Hz, 1H); 7.00 (d, *J* = 8.2 Hz, 1H); 6.65 (d, *J* = 8.5 Hz, 1H); 6.50 (d, *J* = 2.1 Hz, 1H); 6.44 (dd, *J* = 2.1, 8.2 Hz, 1H); 4.10 (m, 1H); 4.07-3.93 (m, 2H); 3.80 (m, 1H); 3.58 (m, 1H); 3.30 (m, 2H, inside the methanol peak); 3.00 (s, 2H); 2.78-2.51 (m, 6H); 1.98-1.80 (m, 4H); 1.75-1.40 (m, 6H).

5 APCI-MS: *m/z* 503(MH⁺).

Example 64

(3*S*)-1-(2-{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)pyrrolidin-3-ol

10

Step I

Methyl 2-{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoate

15 A mixture of 5-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidin] (195 mg, 0.87 mmol) and methyl 4-[(4-methoxybenzyl)oxy]-2-[(2*S*)-oxiran-2-ylmethoxy]benzoate (300 mg, 0.87 mmol) in ethanol (4 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH₄OH) to give the subtitled compound (450 mg).

20 ¹H-NMR (CDCl₃, 400 MHz): δ 7.89-7.85 (m, 1H); 7.39-7.35 (m, 2H); 7.26 (dd, *J* = 1.8, 8.1 Hz, 1H); 7.20 (br, s, 1H); 7.08 (d, *J* = 8.0 Hz, 1H); 6.97-6.93 (m, 2H); 6.64-6.59 (m, 2H); 5.08 (s, 4H); 4.24-4.15 (m, 2H); 4.03 (dd, *J* = 5.8, 9.0 Hz, 1H); 3.88 (s, 3H); 3.84 (s, 3H); 2.98-2.85 (m, 2H); 2.75-2.46 (m, 4H); 2.03-1.90 (m, 2H); 1.77 (br, d, *J* = 13.5 Hz, 2H).
APCI-MS: *m/z* 570(MH⁺).

25 Step II

2-{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoic acid (hydrochloride)

30 Methyl 2-{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoate (450 mg, 0.792 mmol) was taken in ethanol (6 mL). Aqueous KOH (2.31 gm KOH in 2.3 mL of H₂O) was added and the

reaction mixture was refluxed for overnight, cooled to 0 °C and the pH was made to 2.0 by addition of aqueous HCl, extracted with ethyl acetate. The organic layer was washed with H₂O, dried over Na₂SO₄, filtered and concentrated to give the subtitled compound (370 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.97-7.93 (m, 1H); 7.39-7.32 (m, 5H); 6.96-6.91 (m, 2H); 6.75-6.70 (m, 2H); 5.10 (s, 4H); 4.48-4.42 (m, 1H); 4.30 (dd, *J* = 4.0, 9.5 Hz, 1H); 4.11 (dd, *J* = 5.3, 9.5 Hz, 1H); 3.81 (s, 3H); 3.80-3.42 (m, 6H); 2.55-2.41 (m, 2H); 1.98-1.88 (m, 2H).

APCI-MS: *m/z* 554(MH⁺).

Step III

(3S)-1-{2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoyl}pyrrolidin-3-ol

A mixture of 2-[[[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoic acid (hydrochloride) (150 mg, 0.254 mmol) and *N,N*-carbonyldiimidazole (54 mg, 0.33 mmol) in DMF (4 mL) was stirred at room temperature for 1 h, 3(S)-pyrrolidin-3-ol (111 mg, 1.27 mmol) in DMF (1.5 mL) was added and the reaction mixture was stirred at room temperature overnight, partitioned between ethyl acetate and water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH₄OH) to give the subtitled compound (100 mg). APCI-MS: *m/z* 623(MH⁺).

Step IV

(3S)-1-(2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-hydroxybenzoyl]pyrrolidin-3-ol

(3S)-1-(2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoyl]pyrrolidin-3-ol (95 mg, 0.152 mmol) was treated with 10% CF₃CO₂H in CH₂Cl₂ (4 mL) at room temperature for 25 min.

The volatiles were removed in vacuo and the residue was purified by silica gel flash

chromatography (0-5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (34 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.31-7.27 (m, 2H); 7.20 (d, *J* = 8.3 Hz, 1H); 7.10 (d, *J* = 8.3 Hz, 1H); 6.52 (t, *J* = 2.5 Hz, 1H); 6.46 (dt, *J* = 2.0 Hz, 1H); 5.02 (s, 2H); 4.49 (m, 0.5 H); 4.38 (m, 0.5 H); 4.20 (m, 1H); 4.08-3.98 (m, 2H); 3.73-3.49 (m, 3H); 3.30 (m, 1H); 3.12 (br.s, 2H); 2.95-2.70 (m, 4H); 2.18-1.75 (m, 6H).

APCI-MS: *m/z* 503(MH⁺).

Example 65

1-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)piperidin-4-ol

Step I

1-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoyl)piperidin-4-ol

A mixture of 2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoic acid (hydrochloride) (150 mg, 0.254 mmol) and *N,N*-carbonyldiimidazole (54 mg, 0.33 mmol) in DMF (4 mL) was stirred at room temperature for 1 h, piperidin-4-ol (77 mg, 0.762 mmol) was added and the reaction mixture was stirred at room temperature overnight, partitioned between ethyl acetate and water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-2.5% methanol in dichloromethane, 0.2% NH₄OH) to give the subtitled compound (70 mg).
APCI-MS: *m/z* 637(MH⁺).

Step II

1-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)piperidin-4-ol

1-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-

hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoyl)piperidin-4-ol (65 mg, 0.102

mmol) was treated with 10% CF₃CO₂H in dichloromethane (3 mL) for 25 min at room temperature. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (26 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.30-7.25 (m, 2H); 7.19 (d, *J* = 8.1 Hz, 1H); 7.07-6.98 (m, 1H); 6.53 (br.s, 1H); 6.45 (d, *J* = 8.2 Hz, 1H); 5.01 (s, 2H); 4.30-3.70 (m, 5H); 3.62-3.10 (m, 3H); 3.00 (br.s, 2H); 2.73-2.50 (m, 4H); 2.10-1.32 (m, 8H).

APCI-MS: *m/z* 517(MH⁺).

Example 66

N-[4-Hydroxy-2-({(2*S*)-2-hydroxy-3-[5-(trifluoromethyl)-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl]propyl}oxy)phenyl]acetamide

A mixture of 4-(acetylamino)-3-[(2*S*)-oxiran-2-ylmethoxy]phenyl acetate (41 mg, 0.155 mmol) and 5-(trifluoromethyl)-3*H*-spiro[1-benzofuran-2,4'-piperidine] (40 mg, 0.155

mmol) in ethanol (2 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2.5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (54 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.57 (d, *J* = 8.7 Hz, 1H); 7.45 (s, 1H); 7.39 (d, *J* = 8.5 Hz, 1H); 6.82 (d, *J* = 8.4 Hz, 1H); 6.48 (d, *J* = 2.5 Hz, 1H); 6.46 (dd, *J* = 2.6, 8.7 Hz, 1H); 4.20-4.14 (m, 1H); 4.05 (dd, *J* = 3.5, 9.9 Hz, 1H); 3.93 (dd, *J* = 6.2, 9.9 Hz, 1H); 3.08 (s, 2H); 2.80-2.55 (m, 6H); 2.13 (s, 3H); 2.02-1.83 (m, 4H).

APCI-MS: *m/z* 481 (MH⁺).

Example 67

(3*S*)-1-(2-({(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy)-4-hydroxybenzoyl)pyrrolidin-3-ylbenzoate

Step I

tert-Butyl (3*S*)-3-(benzoyloxy)pyrrolidine-1-carboxylate

To a solution of (3S)-pyrrolidin-3-ol (0.87 g, 10.0 mmol) in THF (20 mL) was slowly added a solution of di-*tert*-butyl dicarbonate (2.18 g, 10.0 mmol) in THF (10 mL) at room temperature. After addition was completed, the reaction mixture was stirred at room temperature overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2.5% methanol in dichloromethane) to give intermediate *tert*-Butyl (3S)-3-hydroxypyrrolidine-1-carboxylate. To a solution of *tert*-butyl (3S)-3-hydroxypyrrolidine-1-carboxylate (900 mg, 4.8 mmol) in CH₂Cl₂ (6 mL) was added Et₃N (699 mg, 6.91 mmol) followed by benzoyl chloride (809 mg, 5.76 mmol) at 0 °C. After addition was completed, the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between CH₂Cl₂ and H₂O. The organic layer was successively washed with aqueous NaHCO₃ and water, dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane) to give the subtitled compound (642 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 8.03 (d, *J* = 7.3 Hz, 2H); 7.59 (t, *J* = 7.3 Hz, 1H); 7.46 (t, *J* = 7.7 Hz, 2H); 5.58 (m, 1H); 3.75-3.45 (m, 4H); 2.20 (s, 2H); 1.50 (s, 9H).

APCI-MS: *m/z* 192 (MH⁺-Boc).

Step II

(3S)-Pyrrolidin-3-yl-benzoate (trifluoroacetate)

tert-Butyl (3S)-3-(benzoyloxy)pyrrolidine-1-carboxylate (635 mg, 2.18 mmol) was treated with 20% CF₃CO₂H in CH₂Cl₂ (20 mL) overnight at room temperature. The volatiles were removed in vacuo to give the subtitled compound (800 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 9.29 (brd, 2H); 8.06 (m, 2H); 7.64-7.59 (m, 1H); 7.47 (t, *J* = 7.9 Hz, 2H); 5.70 (m, 1H); 3.72-3.50 (m, 4H); 2.40 (m, 2H).

APCI-MS: *m/z* 192 (MH⁺).

Step III

(3S)-1-{2-[[[(2S)-3-(5-Chloro-1'*H*.3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoyl}pyrrolidin-3-yl-benzoate

A mixture of 2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)benzoic acid (hydrochloride) (218 mg, 0.369 mmol) and *N,N*-carbonyldiimidazole (77.5 mg, 0.478 mmol) in DMF (3 mL) was stirred at room temperature for 50 min. Then (3S)-pyrrolidin-3-yl-benzoate (trifluoroacetate) (225 mg, 0.738 mmol) in DMF (1 mL) was added followed by Et₃N (0.102 mL, 0.738 mmol) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-2.5% methanol in dichloromethane) to give the subtitled compound (140 mg).

APCI-MS: *m/z* 727 (MH⁺).

Step IV

(3S)-1-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)pyrrolidin-3-ylbenzoate

(3S)-1-{2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoyl}pyrrolidin-3-yl-benzoate (135 mg, 0.185 mmol) was treated with 10% CF₃CO₂H in CH₂Cl₂ (3 mL) for 35 min. at room temperature. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3.5% methanol in dichloromethane) to give the titled compound (73 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 8.06 (d, *J* = 7.4 Hz, 1H); 8.00 (d, *J* = 7.4 Hz, 1H); 7.61-7.56 (m, 1H); 7.52-7.43 (m, 2H); 7.17-7.04 (m, 3H); 6.71 (dd, *J* = 2.4, 8.5 Hz, 1H); 6.56-6.45 (m, 2H); 5.16 (m, 0.5H); 5.50 (m, 0.5 H); 4.45 (m, 1H); 4.05-3.48 (m, 7H); 3.33-2.92 (m, 8H); 2.40-1.95 (m, 5H).

APCI-MS: *m/z* 607 (MH⁺).

Example 68

(3S)-1-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorobenzoyl)pyrrolidin-3-ol

Step I**Methyl 4-fluoro-2-[(2S)-oxiran-2-ylmethoxy]benzoate**

A mixture of methyl 4-fluoro-2-hydroxybenzoate (456.3 mg, 1.76 mmol), (2S)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (300 mg, 1.76 mmol) and Cs₂CO₃ (687.4 mg, 2.11 mmol) in DMF (4.5 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and H₂O, organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was opurified by silica gel flash chromatography (0-30% ethyl acetate in petroleum spirit) to give the subtitled compound (385 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 7.93-7.85 (m, 1H); 6.77-6.69 (m, 2H); 4.36 (dd, *J* = 2.6, 11.2 Hz, 1H); 4.08 (dd, *J* = 4.9, 11.2 Hz, 1H); 3.90 (s, 3H); 3.44 (m, 1H); 2.95 (m, 2H). APCI-MS: *m/z* 227 (MH⁺).

Step II**Methyl 2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorobenzoate**

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (224 mg, 1.0 mmol), methyl 4-fluoro-2-[(2S)-oxiran-2-ylmethoxy]benzoate (226 mg, 1.0 mmol) in ethanol (2 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2.5% methanol in dichloromethane) to give the subtitled compound (290 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 7.90 (m, 1H); 7.12 (s, 1H); 7.07 (dd, *J* = 2.2, 8.4 Hz, 1H); 6.77-6.67 (m, 3H); 4.25-4.14 (m, 2H); 4.06 (dd, *J* = 5.6, 9.0 Hz, 1H); 3.90 (s, 3H); 3.00 (s, 2H); 2.90-2.60 (m, 6H); 2.00 (m, 2H); 1.86 (m, 2H).

APCI-MS: *m/z* 452 (MH⁺).

Step III**2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorobenzoic acid (hydrochloride)**

Methyl 2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorobenzoate (286 mg, 0.635 mmol) in THF (3 mL) was treated with aqueous KOH (106 mg KOH in 1 mL H₂O) at room temperature for 7 h. The reaction mixture was cooled to 0 °C and pH was made to 2 by addition of aqueous HCl, extracted with ethyl acetate. The organic layer was washed with H₂O, dried over Na₂SO₄, filtered and concentrated to give the subtitled compound (250 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.98 (dd, *J* = 6.9, 8.8 Hz, 1H); 7.20 (s, 1H); 7.11 (dd, *J* = 2.0, 8.6 Hz, 1H); 6.97 (dd, *J* = 2.3, 10.9 Hz, 1H); 6.86-6.79 (m, 1H); 6.74 (d, *J* = 8.5 Hz, 1H); 4.50-4.43 (m, 1H); 4.27 (dd, *J* = 4.0, 9.6 Hz, 1H); 4.13 (dd, *J* = 5.3, 9.6 Hz, 1H); 3.80-3.43 (m, 6H); 3.15 (s, 2H); 2.10 (m, 2H); 2.18 (m, 2H).

APCI-MS: *m/z* 436 (MH⁺).

Step IV

(3S)-1-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorobenzoyl)pyrrolidin-3-ol

A mixture of 2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorobenzoic acid (hydrochloride) (200 mg, 0.423 mmol) and *N,N*-carbonyldiimidazole (89.2 mg, 0.55 mmol) in DMF (3 mL) was stirred at room temperature for 50 min. Then (3S)-pyrrolidin-3-ol (184 mg, 2.11 mmol) in DMF (1 mL) was added and the reaction mixture was stirred at room temperature overnight, partitioned between ethyl acetate and H₂O. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-2.5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (60 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.28 (m, 1H); 7.13 (s, 1H); 7.07-7.02 (m, 1H); 6.97-6.91 (m, 1H); 6.81-6.75 (m, 1H); 6.65 (d, *J* = 8.5 Hz, 1H); 4.49 (m, 0.5H); 4.38 (m, 0.5H); 4.16-3.99 (m, 3H); 3.70 (dd, *J* = 5.2, 9.3 Hz, 1H); 3.64-3.46 (m, 2H); 3.37-3.19 (m, 1H); 3.00 (s, 2H); 2.75-2.52 (m, 6H); 2.14-1.78 (m, 6H).

APCI-MS: *m/z* 506 (MH⁺).

Example 69

(3S)-1-[4-Hydroxy-2-((2S)-2-hydroxy-3-[5-(trifluoromethyl)-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl]propyl)oxy)benzoyl]pyrrolidin-3-ol

Step I

5 Methyl-2-((2S)-2-hydroxy-3-[5-(trifluoromethyl)-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl]propyl)oxy)-4-[(4-methoxybenzyl)oxy]benzoate

A mixture of 5-(trifluoromethyl)-3*H*-spiro[1-benzofuran-2,4'-piperidine] (107 mg, 0.416 mmol) and methyl 4-[(4-methoxybenzyl)oxy]-2-[(2S)-oxiran-2-ylmethoxy]benzoate (143.25 mg, 0.416 mmol) in ethanol (2 mL) was stirred at 75 °C over the weekend. The
10 volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2.5% methanol in dichloromethane) to give the subtitled compound (200 mg).

APCI-MS: *m/z* 602 (MH⁺).

15 Step II

2-((2S)-2-Hydroxy-3-[5-(trifluoromethyl)-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl]propyl)oxy)-4-[(4-methoxybenzyl)oxy]benzoic acid (hydrochloride)

Methyl-2-((2S)-2-hydroxy-3-[5-(trifluoromethyl)-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl]propyl)oxy)-4-[(4-methoxybenzyl)oxy]benzoate (190 mg, 0.315 mmol)
20 was taken in ethanol (4 mL), aqueous KOH (918 mg KOH in 1 mL H₂O) was added and the reaction mixture was stirred at reflux temperature overnight, cooled to 0 °C and pH was made to 2 by addition of aqueous HCl, extracted with ethyl acetate. The organic layer was washed with H₂O, dried over Na₂SO₄, filtered and concentrated to give the subtitled compound (170 mg).

25 ¹H-NMR (CD₃OD, 400 MHz): δ 7.93 (d, *J* = 9.0 Hz, 1H); 7.52 (s, 1H); 7.45 (d, *J* = 8.6 Hz, 1H); 7.36 (d, *J* = 8.6 Hz, 2H); 6.96-6.88 (m, 3H); 6.75-6.69 (m, 2H); 5.10 (s, 2H); 4.44 (m, 1H); 4.28 (dd, *J* = 4.0, 9.5 Hz, 1H); 4.11 (dd, *J* = 5.3, 9.5 Hz, 1H); 3.80 (s, 3H); 3.77-3.43 (m, 6H); 3.22 (s, 2H); 2.38 (m, 2H); 2.20 (m, 2H).

APCI-MS: *m/z* 588 (MH⁺).

Step III

(3S)-1-{2-({(2S)-2-Hydroxy-3-[5-(trifluoromethyl)-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl]propyl}oxy)-4-[(4-methoxybenzyl)oxy]benzoyl}pyrrolidin-3-ol

A mixture of 2-({(2S)-2-hydroxy-3-[5-(trifluoromethyl)-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl]propyl}oxy)-4-[(4-methoxybenzyl)oxy] benzoic acid(hydrochloride) (150
5 mg, 0.24 mmol) and *N,N*-carbonyldiimidazole (47 mg, 0.288 mmol) in DMF (3 mL) was stirred at room temperature for 50 min. Then (3S)-pyrrolidin-3-ol (104.5 mg, 1.2 mmol) in DMF (1 mL) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and H₂O. The
10 organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-2.5% methanol in dichloromethane, 0.2% NH₄OH) to give the subtitled compound (80 mg).

APCI-MS: *m/z* 657 (MH⁺).

15 Step IV

3S)-1-[4-Hydroxy-2-({(2S)-2-hydroxy-3-[5-(trifluoromethyl)-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl]propyl}oxy)benzoyl]pyrrolidin-3-ol

(3S)-1-{2-({(2S)-2-Hydroxy-3-[5-(trifluoromethyl)-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl]propyl}oxy)-4-[(4-methoxybenzyl)oxy]benzoyl}pyrrolidin-3-ol (75 mg,
20 0.114 mmol) was treated with 10% CF₃CO₂H in CH₂Cl₂ (3 mL) for 20 min at room temperature. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (26 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.45 (s, 1H); 7.39 (d, *J* = 8.5 Hz, 1H); 7.09 (dd, *J* = 2.4, 8.2 Hz, 1H); 6.82 (d, *J* = 8.4 Hz, 1H); 6.50 (m, 1H); 6.45 (m, 1H); 4.48 (m, 0.5 H); 4.36 (m, 0.5H); 4.15-4.01 (m, 2H); 3.97 (dd, *J* = 5.6, 9.7 Hz, 1H); 3.72-3.50 (m, 3H); 3.38-3.23 (m, 1H); 3.06 (s, 2H); 2.79-2.52 (m, 6H); 2.12-1.80 (m, 6H).

APCI-MS: *m/z* 537 (MH⁺).

30 Example 70

(3S)-1-(4-Fluoro-2-(((2S)-2-hydroxy-3-(1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl)oxy}benzoyl)pyrrolidin-3-ol

Step I

5 **Methyl-4-fluoro-2-(((2S)-2-hydroxy-3-(1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl)oxy}benzoate**

A mixture of 3*H*-spiro[1-benzofuran-2,4'-piperidine] (55 mg, 0.29 mmol) and methyl 4-fluoro-2-((2*S*)-oxiran-2-ylmethoxy)benzoate (66 mg, 0.29 mmol) in ethanol (1.5 mL) was stirred at 78 °C overnight. The volatiles were removed in vacuo and the residue was
10 purified by silica gel flash chromatography (0-1% methanol in dichloromethane) to give the subtitled compound (50 mg).

APCI-MS: *m/z* 416 (*MH*⁺).

Step II

15 **4-Fluoro-2-(((2S)-2-hydroxy-3-(1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl)oxy}benzoic acid (hydrochloride)**

Methyl-4-fluoro-2-(((2*S*)-2-hydroxy-3-(1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl)oxy}benzoate (50 mg, 0.12 mmol) was dissolved in THF (1.5 mL). Aqueous KOH (20 mg KOH in 0.5 mL H₂O) was added and the reaction mixture was stirred at room
20 temperature for 24 h, cooled to 0 °C and pH was adjusted to 2 by addition of aqueous HCl, extracted with ethyl acetate. The organic layer was washed with H₂O, dried over Na₂SO₄, filtered and concentrated to give the subtitled compound (37 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.96 (dd, *J* = 6.9, 8.8 Hz, 1H); 7.20 (d, *J* = 7.2 Hz, 1H); 7.12 (t, *J* = 7.5 Hz, 1H); 6.97 (dd, *J* = 2.4, 11.0 Hz, 1H); 6.88-6.78 (m, 2H); 6.76 (d, *J* = 8.0
25 Hz, 1H); 4.43 (m, 1H); 4.27 (dd, *J* = 4.1, 9.5 Hz, 1H); 4.13 (dd, *J* = 5.3, 9.5 Hz, 1H); 3.79-3.42 (m, 6H); 3.14 (s, 2H); 2.30 (m, 2H); 2.16 (m, 2H).

APCI-MS: *m/z* 402 (*MH*⁺).

Step III

(3S)-1-(4-Fluoro-2-{[(2S)-2-hydroxy-3-(1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}benzoyl)pyrrolidin-3-ol

A mixture of 4-fluoro-2-{[(2S)-2-hydroxy-3-(1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}benzoic acid (hydrochloride) (35 mg, 0.079 mmol) and *N,N*-carbonyldiimidazole (15.4 mg, 0.095 mmol) in DMF (1.5 mL) was stirred at room temperature for 45 min, (3S)-pyrrolidin-3-ol (34.4 mg, 0.395 mmol) in DMF (0.5 mL) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and H₂O. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-2.5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (15 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.32-7.26 (m, 1H); 7.13 (d, *J* = 7.3 Hz, 1H); 7.05 (t, *J* = 7.6 Hz, 1H); 6.94 (dt, *J* = 2.2 Hz, 1H); 6.82-6.75 (m, 2H); 6.67 (d, *J* = 7.9 Hz, 1H); 4.48 (m, 0.5H); 4.38 (m, 0.5H); 4.18-3.98 (m, 3H); 3.70 (dd, *J* = 5.3, 9.3 Hz, 1H); 3.66-3.46 (m, 2H); 3.37-3.18 (m, 1H); 3.00 (s, 2H); 2.78-2.51 (m, 6H); 2.15-1.78 (m, 6H).

APCI-MS: *m/z* 471 (MH⁺).

Example 71

4-Fluoro-2-{[(2S)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}benzoic acid (hydrochloride)

Step I

Methyl-4-fluoro-2-{[(2S)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}benzoate

A mixture of 5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (50 mg, 0.241 mmol) and methyl 4-fluoro-2-[(2S)-oxiran-2-ylmethoxy]benzoate (54.5 mg, 0.241 mmol) in ethanol (1.5 mL) was stirred at 77 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2.5% methanol in dichloromethane) to give the subtitled compound (80 mg).

APCI-MS: *m/z* 434 (MH⁺).

Step II**4-Fluoro-2-([(2S)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}benzoic acid (hydrochloride)**

5 To a solution of methyl 4-fluoro-2-([(2S)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}benzoate (80 mg, 0.184 mmol) in THF (1.5 mL) was added aqueous KOH solution (31 mg KOH in 0.5 mL of H₂O) and the reaction mixture was stirred at room temperature for 24 h, cooled to 0 °C and pH was adjusted to 2 by addition of aqueous HCl, extracted with ethyl acetate. The organic layer was washed
10 with H₂O, dried over Na₂SO₄, filtered and concentrated to give the titled compound (60 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.97 (dd, *J* = 6.9, 8.7 Hz, 1H); 6.97 (m, 2H); 6.88-6.79 (m, 2H); 6.72 (dd, *J* = 4.2, 8.8 Hz, 1H); 4.45 (m, 1H); 4.27 (dd, *J* = 4.1, 9.6 Hz, 1H); 4.13 (dd, *J* = 5.3, 9.6 Hz, 1H); 3.78-3.42 (m, 6H); 3.14 (s, 2H); 2.30 (m, 2H); 2.16 (m, 2H).

15 APCI-MS: *m/z* 420 (MH⁺).

Example 72**(3S)-1-(4-Fluoro-2-([(2S)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}benzoyl)pyrrolidin-3-ol**

20 A mixture of 4-fluoro-2-([(2S)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}benzoic acid (hydrochloride) (50 mg, 0.109 mmol) and *N,N*-carbonyldiimidazole (21.2 mg, 0.131 mmol) in DMF (1.5 mL) was stirred at room temperature for 1 h, (3S)-pyrrolidin-3-ol (47.5 mg, 0.545 mmol) in DMF (0.5 mL) was added and the reaction mixture was stirred at room temperature overnight. The reaction
25 mixture was partitioned between ethyl acetate and H₂O. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-2.5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (21 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.29 (m, 1H); 6.97-6.87 (m, 2H); 6.82-6.74 (m, 2H); 6.93 (dd, *J* = 4.1, 8.7 Hz, 1H); 4.48 (m, 0.5H); 4.37 (m, 0.5H); 4.16-3.98 (m, 3H); 3.70 (dd, *J* =
30

5.3, 9.4 Hz, 1H); 3.67-3.47 (m, 2H); 3.36-3.18 (m, 1H); 3.05 (s, 2H); 2.78-2.52 (m, 6H); 2.16-1.78 (m, 6H).

APCI-MS: m/z 489 (MH^+).

5 **Example 73**

N-[(3S)-1-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)pyrrolidin-3-yl]acetamide

Step I

10 *N*-[(3S)-1-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoyl]pyrrolidin-3-yl]acetamide

A mixture of 2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)benzoic acid (hydrochloride) (150 mg, 0.254 mmol) and *N,N*-carbonyldiimidazole (50 mg, 0.308 mmol) in DMF (2 mL) was stirred at
15 room temperature for 50 min. Then, *N*-[(3S)-pyrrolidin-3-yl]acetamide (110 mg, 1.26 mmol) in DMF (0.5 mL) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane) to
20 give the subtitled compound (100 mg).

APCI-MS: m/z 664 (MH^+).

Step II

N-[(3S)-1-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)pyrrolidin-3-yl]acetamide
25

N-[(3S)-1-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoyl]pyrrolidin-3-yl] acetamide (100 mg, 0.15 mmol) was treated with 10% CF_3CO_2H in CH_2Cl_2 (3 mL) for 25 min at room temperature. The volatiles were removed in vacuo and the residue was purified by silica

gel flash chromatography (0-4% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (22 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.13 (m, 1H); 7.09 (dd, *J* = 3.7, 8.2 Hz, 1H); 7.04 (dd, *J* = 1.7, 8.5 Hz, 1H); 6.65 (d, *J* = 8.5 Hz, 1H); 6.50 (t, *J* = 2.0 Hz, 1H); 6.45 (dt, *J* = 2.2 Hz, 1H); 4.44 (m, 0.5H); 4.26 (m, 0.5H); 4.16-3.77 (m, 3H); 3.74-3.58 (m, 2H); 3.52-3.14 (m, 2H); 3.00 (s, 2H); 2.77-2.52 (m, 6H); 2.28-2.10 (m, 1H); 1.98-1.78 (m, 8H).

APCI-MS: *m/z* 545 (MH⁺).

Example 74

2- $\{[(2S)$ -3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-methylbenzoic acid (hydrochloride)

Step I

Methyl 4-methyl-2-[(2*S*)-oxiran-2-ylmethoxy]benzoate

A mixture of (2*S*)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (777.7 mg, 3.0 mmol), methyl 2-hydroxy-4-methylbenzoate ((498.5 mg, 3.0 mmol) and Cs₂CO₃ (1.17 g, 3.6 mmol) in DMF (10 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and H₂O. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-20% ethyl acetate in petroleum spirit) to give the subtitled compound (500 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 7.75 (d, *J* = 7.9 Hz, 1H); 6.84 (d, *J* = 7.9 Hz, 1H); 6.81 (s, 1H); 4.33 (dd, *J* = 3.0, 11.2 Hz, 1H); 4.12 (dd, *J* = 4.8, 11.2 Hz, 1H); 3.89 (s, 3H); 3.42 (m, 1H); 2.94 (m, 2H); 2.38 (s, 3H).

APCI-MS: *m/z* 223 (MH⁺).

Step II

Methyl 2- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-methylbenzoate

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidin] (223.7 mg, 1.0 mmol) and methyl 4-methyl-2-[(2*S*)-oxiran-2-ylmethoxy]benzoate (222.24 mg, 1.0 mmol) in ethanol

(2 mL) was stirred at 80 °C for 5h. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane) to give the subtitled compound (410 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 7.76 (d, *J* = 8.4 Hz, 1H); 7.13 (s, 1H); 7.08 (dd, *J* = 2.2, 8.5 Hz, 1H); 6.85 (m, 2H); 6.68 (d, *J* = 8.4 Hz, 1H); 4.24 (m, 1H); 4.19 (dd, *J* = 4.3, 9.2 Hz, 1H); 4.08 (dd, *J* = 6.0, 9.1 Hz, 1H); 3.90 (s, 3H); 3.02 (s, 2H); 2.94-2.67 (m, 6H); 2.40 (s, 3H); 2.06-1.86 (m, 4H).

APCI-MS: *m/z* 448 (MH⁺).

Step III

2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-methylbenzoic acid (hydrochloride)

Methyl 2-[[[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-methylbenzoate (400 mg, 0.89 mmol) was taken in ethanol, aqueous KOH (2.6 g KOH in 2.6 mL H₂O) solution was added and the reaction mixture was stirred at reflux temperature for 5h, cooled to 0 °C and the pH was made to 2 by addition of aqueous HCl, extracted with ethyl acetate. The organic layer was washed with H₂O, dried over Na₂SO₄, filtered and concentrated to give the titled compound (330 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.82 (d, *J* = 7.9 Hz, 1H); 7.20 (s, 1H); 7.10 (dd, *J* = 2.2, 8.5 Hz, 1H); 6.98 (s, 1H); 6.90 (d, *J* = 8.1 Hz, 1H); 6.74 (d, *J* = 8.5 Hz, 1H); 4.44 (m, 1H); 4.29 (dd, *J* = 4.0, 9.5 Hz, 1H); 4.12 (dd, *J* = 5.4, 9.6 Hz, 1H); 3.78-3.42 (m, 6H); 3.14 (s, 2H); 2.40 (s, 3H); 2.30 (m, 2H); 2.16 (m, 2H).

APCI-MS: *m/z* 432 (MH⁺).

Example 75

(3S)-1-(2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]]-4-methylbenzoyl)pyrrolidin-3-ol

A mixture of 2-[[[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-methylbenzoic acid (hydrochloride) (150 mg, 0.32 mmol) and *N,N*-carbonyldiimidazole (65 mg, 0.4 mmol) in DMF (2.5 mL) was stirred at room temperature

for 45 min. Then (3S)-pyrrolidin-3-ol (139.4 mg, 1.6 mmol in DMF (0.5 mL) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and H₂O. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-
5 2.5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (90 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.13 (m, 2H); 7.04 (dd, *J* = 2.1, 8.5 Hz, 1H); 6.92 (s, 1H); 6.85 (d, *J* = 7.6 Hz, 1H); 6.60 (d, *J* = 8.5 Hz, 1H); 4.47 (m, 0.5H); 4.35 (m, 0.5H); 4.17-3.96 (m, 3H); 3.74-3.44 (m, 3H); 3.37-3.18 (m, 1H); 3.00 (s, 2H); 2.77-2.50 (m, 6H); 2.36 (s, 3H); 2.14-1.78 (m, 6H).

10 APCI-MS: *m/z* 501 (MH⁺).

Example 76

2-[[[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-methylbenzoic acid (hydrochloride)

15

Step I

Methyl2-[[[(2S)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-methylbenzoate

A mixture of 5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidin] (85 mg, 0.41 mmol) and
20 methyl4-methyl-2-[(2S)-oxiran-2-ylmethoxy]benzoate (91 mg, 0.41 mmol) in ethanol (2 mL) was stirred at 85 °C for 4.5 h. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2.5% methanol in dichloromethane) to give the subtitled compound (136 mg).

APCI-MS: *m/z* 430 (MH⁺).

25

Step II

2-[[[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-methylbenzoic acid (hydrochloride)

Methyl2-[[[(2S)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-
30 hydroxypropyl]oxy]-4-methylbenzoate (133 mg, 0.309 mmol) was taken in ethanol (2.5

mL), aqueous KOH (902 mg KOH in 1 mL H₂O) was added. The reaction mixture was stirred at reflux temperature for 5 h, cooled to 0 °C and the pH was adjusted to 2 by addition of aqueous HCl, extracted with ethyl acetate. The organic layer was washed with H₂O, dried over Na₂SO₄, filtered and concentrated to give the titled compound (50 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.74 (d, *J* = 7.9 Hz, 1H); 6.96 (m, 2H); 6.89 (d, *J* = 8.0 Hz, 1H); 6.84 (m, 1H); 6.71 (dd, *J* = 4.1, 8.7 Hz, 1H); 4.43 (m, 1H); 4.28 (dd, *J* = 4.0, 9.4 Hz, 1H); 4.11 (dd, *J* = 5.6, 9.5 Hz, 1H); 3.75-3.40 (m, 6H); 3.14 (s, 2H); 2.39 (s, 3H); 2.32 (m, 2H); 2.14 (m, 2H).

APCI-MS: *m/z* 416 (MH⁺).

Example 77

(2S)-1-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-(2-{[2-(hydroxymethyl)morpholin-4-yl]carbonyl}-5-methylphenoxy)propan-2-ol

Step I

4-(*tert*-Butyl)2-methyl 2,4-morpholinedicarboxylate

Methyl iodide (9.38 mL, 150 mmol) was added to a suspension of 4(*tert*-butoxycarbonyl)-2-morpholinecarboxylic acid (14.5 g, 62.6 mmol) and dry K₂CO₃ (17.3 g, 125 mmol) in dry DMF (360 mL). The mixture was stirred overnight at room temperature, filtered through celite and concentrated. The residue was partitioned between CH₂Cl₂ and H₂O. The organic layer was dried over Na₂SO₄ filtered and concentrated to give the subtitled compound (22 g).

¹H-NMR (CDCl₃, 400 MHz): δ 4.07 (dd, 2H); 3.99 (m, 1H); 3.77 (s, 3H); 3.73 (m, 1H); 3.55 (m, 1H); 3.07 (m, 2H); 1.45 (s, 9H).

Step II

Tert-Butyl 2-(hydroxymethyl)-4-morpholinecarboxylate

4-(*tert*-Butyl)2-methyl 2,4-morpholinedicarboxylate (62.6 mmol) was dissolved in dry THF (100 mL) and added drop wise at 0 °C to a suspension of lithium borohydride (2.5 g, 115 mmol) in dry THF (100 mL). After addition was completed the reaction mixture was

stirred at room temperature overnight. Water (10 mL) was added and stirred at room temperature for 1 h. The volatiles were removed in vacuo and the residue was partitioned between ethyl acetate and H₂O. The organic layer was washed successively with 0.5M aqueous HCl, saturated aqueous NaHCO₃ and H₂O. The organic layer was dried over Na₂SO₄, filtered and concentrated to give the subtitled compound (13.3 g).

¹H-NMR (CDCl₃, 400 MHz): δ 3.88 (m, 3H); 3.46-3.42 (m, 4H); 2.93 (m, 1H); 2.75 (m, 1H); 2.09 (m, 1H); 1.46 (s, 9H).

Step III

Morpholin-2-ylmethyl trifluoroacetate (trifluoroacetic acid salt)

Tert-Butyl 2-(hydroxymethyl)-4-morpholinecarboxylate (5.13 g, 23.61 mmol) was treated with CF₃CO₂H (20 mL) in CH₂Cl₂ (50 mL) at room temperature for 3 h. The volatiles were removed in vacuo to give the subtitled compound (7.6 g).

¹H-NMR (DMSO-d₆, 400 MHz): δ 9.25 (br.s, 2H); 3.86 (dd, *J* = 3.3, 12.6 Hz, 1H); 3.62 (m, 2H); 3.39 (m, 2H); 3.19 (m, 2H); 2.96 (t, *J* = 11.2 Hz, 1H); 2.76 (t, *J* = 11.2 Hz, 1H).

Step IV

2S)-1-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-(2-{[2-(hydroxymethyl)morpholin-4-yl]carbonyl}-5-methylphenoxy)propan-2-ol

A mixture of 2-{{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-methylbenzoic acid (hydrochloride) (100 mg, 0.213 mmol) and *N,N*-carbonyldiimidazole (41.5 mg, 0.255 mmol) in DMF (2.5 mL) was stirred at room temperature for 50 min, morpholin-2-ylmethyl trifluoroacetate (trifluoroacetic acid salt) (347 mg, 1.06 mmol) in DMF (1 mL) was added followed by Et₃N (0.3 mL) and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was partitioned between ethyl acetate and H₂O. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-2.5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (58 mg). APCI-MS: *m/z* 531 (MH⁺).

Example 78

(3S)-1-(2-([(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-methylbenzoyl)pyrrolidin-3-ol

A mixture of 2-([(2S)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-methylbenzoic acid (hydrochloride) (45 mg, 0.099 mmol) and *N,N*-carbonyldiimidazole (20 mg, 0.123 mmol) in DMF (2 mL) was stirred at room temperature for 50 min, (3S)-pyrrolidin-3-ol (43 mg, 0.495 mmol) in DMF (1 mL) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and H₂O. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-2.5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (35 mg).
¹H-NMR (CD₃OD, 400 MHz): δ 7.14 (dd, *J* = 1.0, 7.6 Hz, 1H); 6.94-6.84 (m, 3H); 6.77 (m, 1H); 6.62 (dd, *J* = 4.2, 8.8 Hz, 1H); 4.48 (m, 0.5H); 4.35 (m, 0.5H); 4.16-3.96 (m, 3H); 3.73-3.43 (m, 3H); 3.38-3.18 (m, 1H); 3.00 (s, 2H); 2.76-2.52 (m, 6H); 2.35 (s, 3H); 2.12-1.77 (m, 6H).

APCI-MS: *m/z* 485 (MH⁺).

Example 79

2-([(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-*N*-([(4R)-2,5-dioxoimidazolidin-4-yl]methyl)-4-hydroxybenzamide

Step I

2-([(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-*N*-([(4R)-2,5-dioxoimidazolidin-4-yl]methyl)-4-[(4-methoxybenzyl]oxy]benzamide

A mixture of 2-([(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-[(4-methoxybenzyl]benzoic acid (hydrochloride) (125 mg, 0.211 mmol) and *N,N*-carbonyldiimidazole (43 mg, 0.264 mmol) in DMF (3 mL) was stirred at room temperature for 40 min. Then, (5R)-5-(aminomethyl)imidazolidine-2,4-dione

(hydrochloride) (150 mg, 0.906 mmol) was added followed by Et₃N (0.54 mL (3.62 mmol) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-
5 2.5% methanol in dichloromethane, 0.2% NH₄OH) to give the subtitled compound (30 mg).

APCI-MS: m/z 665 (MH⁺).

Step II

10 2- $\{[(2S)-3-(5\text{-Chloro-}1'H,3H\text{-spiro}[1\text{-benzofuran-}2,4'\text{-piperidin-}1'\text{-yl)-}2\text{-hydroxypropyl]oxy}\}-N-\{[(4R)-2,5\text{-dioxoimidazolidin-}4\text{-yl]methyl}\}-4\text{-hydroxybenzamide}$

2- $\{[(2S)-3-(5\text{-Chloro-}1'H,3H\text{-spiro}[1\text{-benzofuran-}2,4'\text{-piperidin-}1'\text{-yl)-}2\text{-hydroxypropyl]oxy}\}-N-\{[(4R)-2,5\text{-dioxoimidazolidin-}4\text{-yl]methyl}\}-4\text{-}[(4\text{-}$

15 methoxybenzyl]oxy]benzamide (28 mg, 0.042 mmol) was treated with 10% CF₃CO₂H in CH₂Cl₂ (3 mL) at room temperature for 25 min. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (9 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.83 (d, J = 8.6 Hz, 1H); 7.14 (s, 1H); 7.04 (dd, J = 1.9, 8.3 Hz, 1H); 6.65 (d, J = 8.5 Hz, 1H); 6.53 (s, 1H); 6.48 (m, 1H); 4.37-4.17 (m, 3H); 4.07
20 (m, 1H); 3.90-3.64 (m, 2H); 3.03 (s, 2H); 2.85-2.59 (m, 6H); 2.02-1.82 (m, 4H).

APCI-MS: m/z 545 (MH⁺).

Example 80

25 1-(2- $\{[(2S)-3-(5\text{-Chloro-}1'H,3H\text{-spiro}[1\text{-benzofuran-}2,4'\text{-piperidin-}1'\text{-yl)-}2\text{-hydroxypropyl]oxy}\}-4\text{-hydroxybenzoyl}\}-3\text{-(trifluoromethyl)pyrrolidin-}3\text{-ol}$

Step I

tert-Butyl 3-hydroxy-3-(trifluoromethyl)pyrrolidine-1-carboxylate

tert-Butyl 3-oxopyrrolidine-1-carboxylate (926 mg, 5.0 mmol) was dissolved in THF (10 mL) and the solution was cooled to 0 °C, trimethyl (trifluoromethyl)silane (0.872 mL) and tetrabutylammonium fluoride (TBAF) (176 mg, 0.557 mmol) were added. The ice-bath was removed and the reaction mixture was stirred at room temperature overnight.

5 Saturated aqueous NH₄Cl solution (8 mL) was added and stirring was continued. After 15 min TBAF (2.36 g TBAF in 7.5 mL THF) was added and the reaction mixture was stirred at room temperature for 1h. The reaction mixture was extracted with ethyl acetate, washed with H₂O, dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-40% ethyl acetate in petroleum spirit) to give the subtitled
10 compound (800 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 3.78-3.38 (m, 4H); 2.25 (m, 1H); 2.00 (m, 1H); 1.40 (s, 9H).

Step II

15 3-(Trifluoromethyl)pyrrolidin-3-ol (trifluoroacetate)

tert-Butyl 3-hydroxy-3-(trifluoromethyl)pyrrolidine-1-carboxylate (310 mg, 1.21 mmol) was treated with 20% CF₃CO₂H in CH₂Cl₂ for 4h at room temperature. The volatiles were removed in vacuo to give the subtitled compound (330 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 3.72-3.59 (m, 4H); 2.38 (m, 1H); 2.22 (m, 1H).

20 APCI-MS: m/z 156 (MH⁺).

Step III

1-{2-[[[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoyl]-3- 25 (trifluoromethyl)pyrrolidin-3-ol

A mixture of 2-[[[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)benzoic acid (hydrochloride) (150 mg, 0.254 mmol) and *N,N*-carbonyldiimidazole (51.5 mg, 0.317 mmol) in DMF (3 mL) was stirred at room temperature for 40 min. Then (3-(trifluoromethyl)pyrrolidin-3-ol (trifluoroacetate)
30 (326 mg, 1.21 mmol) was added followed by Et₃N (0.337 mL, 2.42 mmol) and the reaction

mixture was stirred at room temperature for 20 h. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-2.0% methanol in dichloromethane, 0.2% NH₄OH) to give the subtitled compound (83 mg).

5 APCI-MS: m/z 691 (MH⁺).

Step IV

1-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)-3-(trifluoromethyl)pyrrolidin-3-ol

10 1-{2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoyl}-3-(trifluoromethyl) pyrrolidin-3-ol (83 mg, 0.12 mmol) was treated with 10% CF₃CO₂H in CH₂Cl₂ (3 mL) for 25 min at room temperature. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% NH₄OH) to
15 give the titled compound (15 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.16-7.09 (m, 2H); 7.05 (m, 1H); 6.66 (d, *J* = 8.5 Hz, 1H); 6.50 (s, 1H); 6.46 (d, *J* = 8.3 Hz, 1H); 4.12 (m, 1H); 4.00 (m, 2H); 3.89-3.40 (m, 4H); 3.02 (s, 2H); 2.87-2.60 (m, 6H); 2.35-1.80 (m, 6H).

APCI-MS: m/z 571 (MH⁺).

20

Example 81

3-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-{[3-(trifluoromethyl)pyrrolidin-1-yl]carbonyl} phenol

25 Step I

***tert*-Butyl 3-(trifluoromethyl)pyrrolidine-1-carboxylate**

To a solution of *tert*-butyl 3-hydroxy-3-(trifluoromethyl)pyrrolidine-1-carboxylate (468 mg, 1.83 mmol) in pyridine (10 mL) was added SOCl₂ (1.71 mL) and the reaction mixture was stirred at reflux temperature under nitrogen for 25 min, cooled to room temperature,

30 H₂O (20 mL) was added, extracted with ethyl acetate. The combined organic layer was

washed with dilute aqueous HCl, saturated aqueous NaHCO₃ and H₂O successively. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was dissolved in ethanol (10 mL), Pd/C (10%) (300 mg) was added and it was hydrogenated at room temperature over the weekend. The catalyst was removed by filtration. The filtrate was
5 concentrated in vacuo to give the subtitled compound (100 mg).

APCI-MS: m/z 140 (MH⁺-Boc).

Step II

3-(Trifluoromethyl)pyrrolidine (trifluoroacetate)

10 *tert*-Butyl 3-(trifluoromethyl)pyrrolidine-1-carboxylate (100 mg, 0.42 mmol) was treated with 20% CF₃CO₂H in CH₂Cl₂ at room temperature overnight. The volatiles were removed in vacuo to give the subtitled compound (106 mg).

APCI-MS: m/z 140 (MH⁺).

15 Step III

(2S)-1-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-(5-[(4-methoxybenzyl)oxy]-2-[[3-(trifluoromethyl)pyrrolidin-1-yl]carbonyl]phenoxy)propan-2-ol

A mixture of 2-[[[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)benzoic acid (hydrochloride) (177 mg, 0.3
20 mmol) and *N,N*-carbonyldiimidazole (61 mg, 0.375 mmol) in DMF (3 mL) was stirred at room temperature for 45 min, 3-(trifluoromethyl) pyrrolidine (trifluoroacetate) (106 mg, 0.42 mmol) in DMF (1 mL) was added followed by Et₃N (0.17 mL, 1.2 mmol) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was
25 partitioned between ethyl acetate and H₂O. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.2% NH₄OH) to give the subtitled compound (89 mg).
APCI-MS: m/z 675 (MH⁺).

30 Step IV.

3-(((2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl)oxy)-4-([3-(trifluoromethyl)pyrrolidin-1-yl]carbonyl) phenol (2S)-1-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-(5-[(4-methoxybenzyl)oxy]-2-([3-(trifluoromethyl)pyrrolidin-1-yl]carbonyl) phenoxy) propan-2-ol (88 mg, 0.13 mmol) was treated with 10% CF₃CO₂H in CH₂Cl₂ (3 mL) for 25 min at room temperature. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (22 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.14 (s, 1H); 7.08 (dd, *J* = 4.3, 8.3 Hz, 1H); 7.05 (m, 1H); 6.66 (d, *J* = 8.5 Hz, 1H); 6.51 (m, 1H); 6.46 (m, 1H); 4.15-3.42 (m, 7H); 3.18 (m, 1H); 3.02 (s, 2H); 2.78-2.52 (m, 6H); 2.34-1.80 (m, 6H).

APCI-MS: *m/z* 555 (MH⁺).

Example 82

N-[2-(Acetylamino)ethyl]-2-(((2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl)oxy)-4-hydroxybenzamide

Step I

N-[2-(Acetylamino)ethyl]-2-(((2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl)oxy)-4-[(4-methoxybenzyl) oxy] benzamide

A mixture of 2-(((2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl)oxy)-4-[(4-methoxybenzyl)benzoic acid (hydrochloride) (100 mg, 0.169 mmol) and *N,N*-carbonyldiimidazole 834 mg, 0.211 mmol) in DMF (3 mL) was stirred at room temperature for 45 min, *N*-(2-aminoethyl) acetamide (86 mg, 0.845 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and H₂O. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH₄OH) to give the subtitled compound (77 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 8.38 (t, *J* = 5.6 Hz, 1H); 8.10 (d, *J* = 8.8 Hz, 1H); 7.36 (d, *J* = 8.6 Hz, 2H); 7.13 (m, 2H); 7.07 (dd, *J* = 2.1, 8.4 Hz, 1H); 6.94 (d, *J* = 8.6 Hz, 2H); 6.73-6.65 (m, 3H); 6.57 (d, *J* = 2.2 Hz, 1H); 5.02 (s, 2H); 4.34 (m, 1H); 4.22 (dd, *J* = 3.0, 9.7 Hz, 1H); 4.00 (dd, *J* = 6.3, 9.7 Hz, 1H); 3.83 (s, 3H); 3.65 (m, 2H); 3.48 (m, 2H); 3.06-2.67 (m, 8H); 2.08 (m, 4H); 1.97 (s, 3H).

APCI-MS: *m/z* 638 (MH⁺).

Step II

N-[2-(Acetylamino)ethyl]-2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzamide

N-[2-(Acetylamino)ethyl]-2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-[(4-methoxybenzyl)oxy] benzamide (72 mg, 0.112 mmol) was treated with 10% CF₃CO₂H in CH₂Cl₂ (3 mL) for 25 min at room temperature. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3.5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (32 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.82 (d, *J* = 8.7 Hz, 1H); 7.14 (s, 1H); 7.04 (dd, *J* = 2.2, 8.5 Hz, 1H); 6.66 (d, *J* = 8.5 Hz, 1H); 6.53 (d, *J* = 2.1 Hz, 1H); 6.49 (dd, *J* = 2.1, 8.7 Hz, 1H); 4.23 (m, 2H); 4.07 (dd, *J* = 7.0, 10.7 Hz, 1H); 3.51 (t, *J* = 6.1 Hz, 2H); 3.39 (t, *J* = 6.1 Hz, 2H); 3.02 (s, 2H); 2.74 (br. s, 4H); 2.64 (d, *J* = 6.0 Hz, 2H); 1.99-1.82 (m, 7H).

APCI-MS: *m/z* 518 (MH⁺).

Example 83

N-(5-chloro-2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-methoxyphenyl)acetamide

Step I:

N-(5-chloro-2-hydroxy-4-methoxyphenyl)acetamide

This compound was prepared as described by Kun Hoe Chung; Kyong Mahn Kim; Jae Nyoung Kim and Eung Kul Ryu, *Synth. Comm.*, 1991, 21 (18&19), 1917-1922, using N-(2-hydroxy-4-methoxyphenyl)acetamide as starting material.

APCI-MS: m/z 216 [MH⁺]

5

Step II:

N-{5-chloro-4-methoxy-2-[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide To a slurry of N-(5-chloro-2-hydroxy-4-methoxyphenyl)acetamide (227 mg, 1.05 mmol) and caesium carbonate (376 mg, 1.25 mmol) in 1-methyl-2-pyrrolidinone (2 mL) was added (2S)-oxirane-2-ylmethyl 3-nitrobenzenesulfonate (301 mg, 1.16 mmol) dissolved 2-methyl-2-pyrrolidine (2 mL) drop wise. The resulting brown slurry was stirred over night, at room temperature. The mixture was partitioned between water and ethyl acetate. The organic phase was dried over magnesium sulphate, filtered and concentrated to yield crude 280 mg (98%) of the titled compound.

10

APCI-MS: m/z 272 [MH⁺]

15

Step III:

N-(5-chloro-2-[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-methoxyphenyl}acetamide

A solution of N-{5-chloro-4-methoxy-2-[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide (101 mg, 0.37 mmol) and 5-chloro-3H-spiro[1-benzofuran-2,4'-piperidine] (83.5 mg, 0.37 mmol) in ethanol (10 mL) was refluxed over night, and then concentrated. The crude material was purified on C18 ("Kromasil" column, 10 μ m, acetonitrile/water 25/75 to 50/50 over 30 min with 0.1% trifluoroacetic acid). Pure fractions were pooled and freeze-dried to give 116 mg (51%) of the title compound as the trifluoroacetate salt.

20

¹H-NMR (400 MHz, (CD₃)₂CO) δ : 8.36 (1H, s); 7.24 (1H, bs); 7.14 (1H, dd); 6.87 (1H, s); 6.76 (1H, d); 4.59-4.52 (1H, m); 4.25-4.15 (2H, m); 3.89-3.40 (6H, m); 3.88 (3H, s); 3.20 (2H, bs); 2.45-2.19 (4H, m); 2.12 (3H, s)

APCI-MS: m/z 495 [MH⁺]

Example 84

(3*S*)-*N*-(5-chloro-2-[[*(2S)*-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)-3-hydroxypyrrolidine-1-carboxamide

5 **Step I:**

(3*S*)-*N*-(5-chloro-2-hydroxyphenyl)-3-hydroxypyrrolidine-1-carboxamide

5-chloro-1,3-benzoxazole-2(3*H*)-one (577 mg, 0.34 mmol) and (3*S*)-pyrrolidin-3-ol (0.6 mL, 0.74 mmol) was heated to 90°C for 2 hrs. The resulting red solidified oil was purified on silica (dichloromethane/methanol) to give the titled compound (768 mg, 88%).

10 APCI-MS: *m/z* 257 [MH⁺]

Step II:

(3*S*)-*N*-{5-chloro-2-[(*2S*)-oxiran-2-ylmethoxy]phenyl}-3-hydroxypyrrolidine-1-carboxamide

15 A solution of (3*S*)-*N*-(5-chloro-2-hydroxyphenyl)-3-hydroxypyrrolidine-1-carboxamide (232 mg, 0.90 mmol), (*2S*)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (234 mg, 0.90 mmol) and caesium carbonate (369 mg, 1.13 mmol) in dimethylformamide (9 mL) was stirred at room temperature, over night. The mixture was partitioned between water and ethyl acetate, and the organic phase was washed twice with water and once with brine, and
20 finally concentrated. The crude material was purified by HPLC on C18 ("Kromasil" column, 10 μ m, acetonitrile/water 35/65 to 85/15 over 30 min), yielding the titled compound (82 mg, 29%).

APCI-MS: *m/z* 313 [MH⁺]

25 **(3*S*)-*N*-(5-chloro-2-[[*(2S)*-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)-3-hydroxypyrrolidine-1-carboxamide**

A solution of (3*S*)-*N*-{5-chloro-2-[(*2S*)-oxiran-2-ylmethoxy]phenyl}-3-hydroxypyrrolidine-1-carboxamide (63.2 mg, 0.20 mmol) and 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (45.4 mg, 0.20 mmol) in isopropanol (8 mL) was stirred at
30 80°C over night. The concentrated crude material was purified by HPLC on C18

("Kromasil" column, 10 μ m, acetonitrile/water 50/50 to 85/15 over 45 min, with 0.1% trifluoroacetic acid). Pure fractions were pooled and freeze-dried to give the title compound (83 mg, 65%) as the trifluoroacetate salt.

¹H-NMR (400 MHz, DMSO-*d*₆) δ : 9.69 (1H, bs); 9.60 (1H, bs); 8.00 (1H, d); 7.39 (1H, bs); 7.29 (1H, bs); 7.16 (1H, d); 7.06 (1H, d); 7.00 (1H, dd); 6.78 (1H, d); 4.41-4.34 (1H, m); 4.32 (1H, bs); 4.09-3.97 (2H, m); 3.62-3.40 (7H, m); 3.36-3.16 (4H, m); 3.10 (2H, s); 2.22-2.03 (3H, m); 2.03-1.90 (1H, m); 1.88-1.79 (1H, m)

APCI-MS: *m/z* 536 [MH⁺]

Example 85

(3*S*)-*N*-(2-([(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)-3-hydroxypyrrolidine-1-carboxamide

The title compound was prepared using 1,3-benzoxazole-2(3*H*)-one by methods analogous to the methods described in Example 84.

¹H-NMR (400 MHz, DMSO-*d*₆) δ : 9.70 (1H, bs); 9.62 (1H, bs); 7.82 (1H, d); 7.36 (1H, s); 7.29 (1H, bs); 7.00 (2H, dt); 6.91 (1H, t); 6.80 (1H, d); 4.41-4.34 (1H, m); 4.32 (1H, bs); 4.09-3.97 (2H, m); 3.62-3.41 (7H, m); 3.35-3.15 (4H, m); 3.10 (2H, s); 2.22-2.03 (3H, m); 2.03-1.90 (1H, m); 1.88-1.79 (1H, m)

APCI-MS: *m/z* 502 [MH⁺]

Example 86

***N*-(2-([(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)-4-hydroxypiperidine-1-carboxamide**

The title compound was prepared using 1,3-benzoxazole-2(3*H*)-one and 4-hydroxypiperidine by methods analogous to the methods described in Example 84.

¹H-NMR (400 MHz, DMSO-*d*₆) δ : 9.67 (1H, bs); 9.60 (1H, bs); 7.81 (1H, s); 7.63 (1H, d); 7.30 (1H, d); 7.15 (1H, d); 7.06-6.98 (2H, m); 6.91 (1H, dt); 6.80 (1H, d); 4.41-4.28 (2H,

m); 4.08-3.95 (2H, m); 3.84-3.75 (2H, m); 3.69 (1H, sept); 3.63-3.41 (3H, m); 3.32-3.04 (4H, m); 3.10 (2H, s); 2.22-1.98 (4H, m); 1.80-1.71 (2H, m); 1.41-1.29 (2H, m)

APCI-MS: m/z 516 [MH⁺]

5 **Example 87**

N-(2-{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)urea trifluoroacetate (salt)

Step I:

10 (2*S*)-3-(2-Aminophenoxy)-1-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propan-2-ol bis(hydrochloride) (salt)

N-(2-{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide (117 mg, 0.27 mmol) was stirred in 1M hydrochloric acid (2 mL) at 100°C for 2h. The solution was diluted with water and freeze
15 dried to give the subtitled compound as a white amorphous solid (112 mg).

¹H-NMR (MeOH-*d*₄, 400 MHz): δ 7.49-7.44 (m, 1H); 7.40 (d, *J* = 8.0 Hz, 1H); 7.25 (d, *J* = 8.4 Hz, 1H); 7.21 (bs, 1H); 7.15-7.09 (m, 2H); 6.75 (d, *J* = 8.4 Hz, 1H); 4.64-4.52 (m, 1H); 4.21 (d, *J* = 4.8 Hz, 2H); 3.84-3.65 (m, 2H); 3.49 (dd, *J* = 10.3, 13.1 Hz, 2H); 3.62-3.38 (m, 2H); 3.16 (bs, 2H); 2.33-2.15 (m, 4H)

20 APCI-MS: m/z 389 (MH⁺)

Step II:

N-(2-{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)urea trifluoroacetate (salt)

25 To (2*S*)-3-(2-aminophenoxy)-1-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propan-2-ol bis(hydrochloride) (46.2 mg, 0.1 mmol) dissolved in acetic acid / water (1 / 1 mL) potassium cyanate (16.2 mg, 0.2 mmol) dissolved in water (0.5 mL) was added. The mixture was stirred at ambient temperature overnight. After purification by preparative HPLC using acetonitrile/water containing 0.1% TFA as mobile phase and freeze drying the
30 titled compound was obtained as a white amorphous solid (43 mg, 78%).

¹H-NMR (400 MHz, acetone-d₆): δ 8.38-8.34 (m, 1H); 7.83 (bs, 1H); 7.25 & 7.21 (s, 1H); 7.14 (d, *J* = 8.4 Hz, 1H); 6.93-6.81 (m, 3H); 6.77 (d, *J* = 8.4 Hz, 1H); 5.95 (bs, 2H); 4.60-4.52 (m, 1H); 4.18 (d, *J* = 9.6 Hz, 1H); 4.07-4.00 (m, 1H); 3.92-3.71 (m, 3H); 3.70-3.40 (m, 3H); 3.30 & 3.22 (s, 2H); 2.44-2.19 (m, 4H)

5 APCI-MS: *m/z* 432 (MH⁺)

Example 88

N-(2-(((2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-hydroxyphenyl)urea trifluoroacetate (salt)

10

Step I:

4-Amino-3-(((2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)phenol bis(trifluoroacetate) (salt)

The compound was prepared analogous to the compound Example 87 Step I from

15

N-(2-(((2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-hydroxyphenyl)acetamide (135 mg, 0.3 mmol) and 1M hydrochloric acid (3 mL). After purification by preparative HPLC using acetonitrile/ water containing 0.1% TFA as mobile phase and freeze drying the subtitled compound was obtained as a white amorphous solid (150 mg).

20

¹H-NMR (MeOH-*d*₄, 400 MHz): δ 7.21 (bs, 1H); 7.18 (d, *J* = 8.8 Hz, 1H); 7.11 (dd, *J* = 2.0, 8.4 Hz, 1H); 6.74 (d, *J* = 8.4 Hz, 1H); 6.62 (d, *J* = 2.4 Hz, 1H); 6.49 (dd, *J* = 2.4, 8.8 Hz, 1H); 4.58-4.49 (m, 1H); 4.13 (d, *J* = 4.8 Hz, 2H); 3.8-3.6 (m, 2H); 3.6-3.4 (m, 2H); 3.48 (d, *J* = 13.2 Hz, 1H); 3.45 (d, *J* = 13.2 Hz, 1H); 3.16 (s, 2H); 2.31-2.17 (m, 4H)
APCI-MS: *m/z* 405 (MH⁺)

25

Step II:

N-(2-(((2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-hydroxyphenyl)urea trifluoroacetate (salt)

The compound was prepared analogous to the compound Example 87 Step II from

4-amino-3-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenol bis(hydrochloride) (63.3 mg, 0.1 mmol) and potassium cyanate (16.2 mg, 0.2 mmol). After purification and freeze drying the titled compound was obtained as a white amorphous solid (51 mg, 90%).

- 5 ¹H-NMR (400 MHz, acetone-*d*₆): δ 8.01 (d, *J* = 8.8 Hz, 1H); 7.60 (s, 1H); 7.25 & 7.21 (s, 1H); 7.14 (dd, *J* = 2.2, 8.4 Hz, 1H); 6.77 (d, *J* = 8.4 Hz, 1H); 6.45 (d, *J* = 2.5 Hz, 1H); 6.37 (dd, *J* = 2.5, 8.8 Hz, 1H); 4.57-4.49 (m, 1H); 4.12 (dd, *J* = 9.7, 2.6 Hz, 1H); 4.01 (dd, *J* = 9.7, 5.1 Hz, 1H); 3.95-3.65 (m, 3H); 3.62-3.40 (m, 3H); 3.33 & 3.21 (s, 3H); 2.44-2.20 (m, 4H)
- 10 APCI-MS: *m/z* 448 (MH⁺)

Example 89

N-(2-{{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorophenyl)urea trifluoroacetate (salt)

15

Step I:

(2*S*)-1-(2-Amino-5-fluorophenoxy)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propan-2-ol bis(hydrochloride) (salt)

The subtitled compound was prepared analogous to the compound Example 87 Step I from

- 20 *N*-(2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorophenyl)acetamide (150 mg, 0.27 mmol) and 1M hydrochloric acid (2 mL).

APCI-MS: *m/z* 407 (MH⁺)

- 25 **Step II:**

N-(2-{{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorophenyl)urea trifluoroacetate (salt)

The reaction solution obtained from Step I was buffered with ammonia acetate (200 mg) dissolved in acetic acid (1 mL). Potassium cyanate (44 mg, 0.54 mmol) dissolved in water (0.5 mL) was added and the mixture was stirred at ambient temperature over night. After

30

purification of the reaction mixture by preparative HPLC using acetonitrile/water containing 0.1% TFA as mobile phase and freeze drying the titled compound was obtained as a white amorphous solid (105 mg).

¹H-NMR (MeOH-*d*₄, 300 MHz): δ 7.70 (dd, *J* = 8.7, 6.3 Hz, 1H); 7.22-7.19 (m, 1H); 7.11 (dd, *J* = 8.4, 2.4 Hz, 1H); 6.86 (dd, *J* = 10.2, 2.7 Hz, 1H); 6.74 (d, *J* = 8.4 Hz, 1H); 6.69 (ddd, *J* = 8.4, 8.4, 2.7 Hz, 1H); 4.53-4.43 (m, 1H); 4.09 (d, *J* = 5.1 Hz, 2H); 3.76-3.62 (m, 2H); 3.56-3.34 (m, 4H); 3.21 & 3.14 (s, 2H); 2.30-2.05 (m, 4H)

APCI-MS: *m/z* 450 (MH⁺)

Example 90

N-{[(2-{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)amino]carbonyl}methanesulfonamide trifluoroacetate (salt)

To a solution of 4-nitrophenyl chloroformate (50 mg, 0.25 mmol) in DCM (3 mL) DMAP (30 mg, 0.25 mmol) was added. After stirring the mixture for 5 min methanesulfonamide (24 mg, 0.25 mmol) and TEA (25 μL, 0.25 mmol) was added and the stirring continued for 1h. 4-Amino-3-{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenol (78 mg, 0.12 mmol) dissolved in DCM (2 mL) and TEA (75 μL, 0.75 mmol) was added and the stirring continued at ambient temperature. The reaction was complete after 2h as monitored by LCMS. After evaporation of the solvent the crude product was purified by preparative HPLC using acetonitrile/water containing 0.1% TFA as mobile phase. The titled compound was obtained as a white amorphous solid (7 mg) after freeze drying.

¹H-NMR (Acetone-*d*₆, 300 MHz): δ 8.32 (bs, 1H); 7.91 (d, *J* = 8.7 Hz, 1H); 7.24 (bs, 1H); 7.14 (dd, *J* = 8.4, 2.2 Hz, 1H); 6.78 (d, *J* = 8.6 Hz, 1H); 6.51 (d, *J* = 2.4 Hz, 1H); 6.43 (dd, *J* = 8.6, 2.6 Hz, 1H); 4.61-4.52 (m, 1H); 4.11 (dd, *J* = 9.5, 3.8 Hz, 1H); 3.98 (dd, *J* = 9.5, 6.4 Hz, 1H); 4.01-3.78 (m, 2H); 3.65 (d, *J* = 9.4 Hz, 1H); 3.74-3.42 (m, 4H); 3.27 (s, 3H); 3.30-3.15 (m, 2H); 2.43-2.20 (m, 4H)

APCI-MS: *m/z* 526 (MH⁺)

Example 91

(4*S*)-2-(2-([(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-hydroxybenzoyl)isoxazolidin-4-ol trifluoroacetate (salt)

Step I:**(*S*)-Methyl 2-[4-hydroxyisoxazolidin-2-yl]carbonylbenzoate**

Triethylamine (0.28 ml) was added to a solution of *N*-hydroxyphthalimide (5.00 g, 30 mmol) and (*R*)-(-)-epichlorohydrin (2.40 ml, 30.6 mmol) in anhydrous dioxane (10ml) under nitrogen. The mixture was stirred at 50°C for 48h, further (2*R*)-2-(chloromethyl)oxirane (0.24 ml) and triethylamine (0.28ml) were added and stirring continued at 50°C for 24 h. Methanol (10ml) and further triethylamine (4.27 ml) were added and stirring continued at 50°C for 2 h. The mixture was evaporated under reduced pressure, the residue dissolved in saturated aqueous sodium bicarbonate solution (100 ml) and extracted with ethyl acetate (6 x 100 ml). Combined organic extracts were dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residue was recrystallised from ethyl acetate to give the sub-title compound (3.4 g).

¹H-NMR (CDCl₃; 400 MHz): δ 3.66 (1H, d, br), 3.79 (1H, d, br), 3.89-3.99 (1H, m), 3.99-4.10 (1H, m), 4.74-4.81 (1H, m), 7.46 (1H, d), 7.49 (1H, t), , 7.62 (1H, t), 7.99 (1H, d)

MS(ESI): m/z 252 [M+H]⁺

Step II:**(*S*)-4-Isoxazolidinol hydrochloride**

Hydrochloric acid (4M, 15ml) was added to (*S*)-Methyl 2-[4-hydroxyisoxazolidin-2-yl]carbonylbenzoate (1.87 g, 7.4 mmol) and the solution heated under reflux for 3 h. The mixture was cooled to room temperature, filtered and evaporated under reduced pressure. The residue was recrystallised from propan-2-ol to give the sub-title compound as white needles (0.78 g).

¹H-NMR (DMSO-*d*₆; 400 MHz): δ 3.35 (1H, d), 3.47 (1H, dd), 4.03 (1H, dd), 4.07 (1H, d), 4.78-4.81 (1H, m).

Step III:

(4*S*)-2-{2-[[[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoyl]isoxazolidin-4-ol

- 5 After stirring PS-carbodiimide (1.28 mmol/g) (312 mg, 0.4 mmol) in DCM (5 mL) for 15 min 2-[[[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoic acid (118 mg, 0.2 mmol) dissolved in DCM (2 mL) was added and stirring continued for 30 min. A solution of (*S*)-4-isoxazolidinol hydrochloride (25 mg, 0.2 mmol) and TEA (70 μ L, 0.5 mmol) in DCM (1
10 mL) was added and stirring continued at ambient temperature over night. The reaction was complete as monitored by LCMS. All solids were filtered off and the filtrate evaporated in vacuo. The residue was partitioned between ethylacetate and water, the organic phase washed with water, dried and evaporated in vacuo leaving an oil (93 mg).

APCI-MS: m/z 625 (MH^+)

15

Step IV:

(4*S*)-2-(2-[[[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-hydroxybenzoyl]isoxazolidin-4-ol trifluoroacetate (salt)

- (4*S*)-2-{2-[[[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoyl]isoxazolidin-4-ol (93 mg, 0.15
20 mmol) was dissolved in a mixture of TFA/DCM 1/9 (10 mL) and the solution stirred at ambient temperature for 30 min. After evaporation of the solvent in vacuo the residue was purified by preparative HPLC using acetonitrile / water containing 0.1% TFA as mobile phase. The titled compound was obtained as a white amorphous solid (18 mg) after freeze
25 drying.

1H -NMR (Acetone- d_6 , 300 MHz): δ 7.23 (bs, 1H); 7.22 (d, J = 8.2 Hz, 1H); 7.14 (dd, J = 8.5, 2.4 Hz, 1H); 6.78 (d, J = 8.5 Hz, 1H); 6.61 (d, J = 2.0 Hz, 1H); 6.50 (dd, J = 8.3, 2.0 Hz, 1H); 4.88-4.81 (m, 1H); 4.60-4.48 (m, 1H); 4.15 (dd, J = 9.5, 4.5 Hz, 1H); 4.02 (dd, J = 9.5, 6.3 Hz, 1H); 3.97 (dd, J = 11.7, 5.9 Hz, 1H); 3.94-3.87 (m, 2H); 3.86-3.72 (bs, 2H);

3.70 (d, $J = 11.7$ Hz, 2H); 3.56-3.40 (bs, 2H); 3.41 (dd, $J = 13.5, 9.2$ Hz, 1H); 3.17 (bs, 2H); 2.48-2.14 (m, 4H)

APCI-MS: m/z 505 (MH^+)

5 **Example 92**

(4*R*)-2-(2-{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)isoxazolidin-4-ol trifluoroacetate (salt)

Step I:

10 **(*R*)-Methyl 2-[4-hydroxyisoxazolidin-2-yl]carbonylbenzoate**

Prepared from (2*S*)-2-(chloromethyl)oxirane by the method of described in Example 91 Step I.

1H -NMR ($CDCl_3$; 400 MHz): δ 3.66 (1H, d, br), 3.79 (1H, d, br), 3.89-3.99 (1H, m), 3.99-4.10 (1H, m), 4.74-4.81 (1H, m), 7.46 (1H, d), 7.49 (1H, t), 7.62 (1H, t), 7.99 (1H, d).

15 MS(ESI): m/z 252 [$M+H$] $^+$

Step II:

(*R*)-4-Isoxazolidinol hydrochloride

Prepared from (*R*)-Methyl 2-[4-hydroxyisoxazolidin-2-yl]carbonylbenzoate following the
20 procedure of Example 91 Step II.

1H -NMR ($CDCl_3$; 400 MHz): δ 3.35 (1H, d), 3.47 (1H, dd), 4.03 (1H, dd), 4.07 (1H, d), 4.78-4.81 (1H, m).

Step III:

25 **(4*R*)-2-{2-{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoyl}isoxazolidin-4-ol**

The subtitled compound was prepared analogous to the compound Example 91 Step III from 2-{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoic acid (118 mg, 0.2 mmol) and (*R*)-
30 4-isoxazolidinol hydrochloride (25 mg, 0.2 mmol).

APCI-MS: m/z 625 (MH^+)

Step IV:

(4R)-2-(2-([(2S)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-hydroxybenzoyl)isoxazolidin-4-ol trifluoroacetate (salt)

The titled compound was prepared analogous to the compound Example 91 Step IV from (4R)-2-(2-([(2S)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-[(4-methoxybenzyl)oxy]benzoyl)isoxazolidin-4-ol

and TFA/DCM 1/9. After purification and freeze drying the titled compound was obtained as a white amorphous solid (26 mg).

1H -NMR (Acetone- d_6 , 300 MHz): δ 7.23 (bs, 1H); 7.22 (d, J = 8.2 Hz, 1H); 7.14 (dd, J = 8.5, 2.4 Hz, 1H); 6.78 (d, J = 8.5 Hz, 1H); 6.61 (d, J = 2.0 Hz, 1H); 6.50 (dd, J = 8.3, 2.0 Hz, 1H); 4.88-4.81 (m, 1H); 4.60-4.48 (m, 1H); 4.15 (dd, J = 9.5, 4.5 Hz, 1H); 4.02 (dd, J = 9.5, 6.3 Hz, 1H); 3.97 (dd, J = 11.7, 5.9 Hz, 1H); 3.94-3.87 (m, 2H); 3.86-3.72 (bs, 2H); 3.70 (d, J = 11.7 Hz, 2H); 3.56-3.40 (bs, 2H); 3.41 (dd, J = 13.5, 9.2 Hz, 1H); 3.17 (bs, 2H); 2.48-2.14 (m, 4H)

APCI-MS: m/z 505 (MH^+)

Example 93

(4S)-2-(2-([(2S)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-hydroxybenzoyl)-4-methylisoxazolidin-4-ol trifluoroacetate (salt)

Step I:

2-([(2S)-2-Methyloxiranyl]methoxy)-1H-isoindole-1,3(2H)-dione

A mixture of N-hydroxyphthalimide (5.3 g, 32.5 mmol), [(2S)-2-methyloxiran-2-yl]methyl 3-nitrobenzenesulfonate (5.9 g, 21.6 mmol) and triethylamine (10.6ml) in dichloromethane (15ml) was stirred under nitrogen at ambient temperature for 24 h. The reaction mixture was poured onto a silica column and eluted with dichloromethane to give the sub-title compound as a colourless solid (3.1g).

¹H-NMR (CDCl₃; 400 MHz): δ 1.63 (3H, s), 2.69 (1H, d), 2.76 (1H, d), 4.17 (1H, d), 4.21 (1H, d), 7.73-7.78 (2H, m), 7.82-7.87 (2H, m)

MS (APCI) 234 [M+H]⁺

5 **Step II:**

2-[[[(2*R*)-3-Chloro-2-hydroxy-2-methylpropyl]oxy]- 1*H*-isoindole-1,3(2*H*)-dione

2-[[[(2*S*)-2-Methyloxiranyl]methoxy]-1*H*-isoindole-1,3(2*H*)-dione (3.0 g, 12.9 mmol) was treated with concentrated hydrochloric acid (12ml) and stirred at ambient temperature for 2 h. The mixture was partitioned between water and dichloromethane, the organics were dried and purified by chromatography (EtOAc) to give the sub-title compound as a colourless solid (3.3g).

¹H-NMR (CDCl₃; 400 MHz): δ 1.29(3H, s), 3.67 (1H, d), 3.76 (1H, d), 4.09 (1H, d), 4.15 (1H, d), 7.86 (4H, s), 5.24 (1H, s)

15 **Step III:**

2-[[[(4*S*)-4-Hydroxy-4-methyl-2-isoxazolidinyl]carbonyl]- benzoic acid methyl ester

A solution of 2-[[[(2*R*)-3-Chloro-2-hydroxy-2-methylpropyl]oxy]- 1*H*-isoindole-1,3(2*H*)-dione (3.3 g, 12.2 mmol) in methanol (25 ml) was treated with triethylamine (3.4 ml) and heated under nitrogen at reflux for 1 h. The mixture was concentrated to dryness and purified by chromatography eluting with a gradient from dichloromethane to 5% methanol in dichloromethane. The chiral purity of the product was enhanced by recrystallising twice from acetonitrile to give the sub-title compound as a colourless solid (1.92 g).

¹H-NMR (CDCl₃; 400 MHz): δ 1.52 (3H, s), 3.59 (1H, d), 3.81 (1H, d), 3.88 (1H, d), 4.04 (1H, s), 4.34 (1H, d), 3.92 (3H, s), 7.45 (1H, d), 7.49 (1H, t), 7.62 (1H, t), 8.00 (1H, d).

25 HPLC: (9010THIP.M) 50mm chiracel AD column, ee >99%

Step IV:

(4*S*)-4-Methyl-4-isoxazolidinol hydrochloride

A solution of 2-[[[(4*S*)-4-Hydroxy-4-methyl-2-isoxazolidinyl]carbonyl]- benzoic acid methyl ester (4.9 g, 19.5 mmol) in 2N hydrochloric acid (30 ml) was heated under nitrogen

at reflux for 4 h. After cooling the precipitate was removed by filtration and the liquors concentrated to dryness under vacuo. The residue was triturated with acetonitrile to give the sub-title compound as a white solid (1.79 g).

¹H-NMR (CDCl₃; 400 MHz): δ 1.42 (3H, s), 3.29 (1H, d), 3.41 (1H, dD), 3.87 (1H, d),
5 4.05 (1H, dd)

Step V:

(4*S*)-2-{2-[[[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoyl}-4-methylisoxazolidin-4-ol

10 The subtitled compound was prepared analogous to the compound Example 91 Step III from 2-[[[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoic acid (118 mg, 0.2 mmol) and (4*S*)-4-methyl-4-isoxazolidinol hydrochloride (28 mg, 0.2 mmol).

APCI-MS: m/z 639 (MH⁺)

Step VI:

(4*S*)-2-(2-[[[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-hydroxybenzoyl)-4-methylisoxazolidin-4-ol trifluoroacetate (salt)

20 The titled compound was prepared analogous to the compound Example 91 Step IV from (4*S*)-2-{2-[[[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoyl}-4-methylisoxazolidin-4-ol (crude product from (4*S*)-2-{2-[[[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoyl}-4-methylisoxazolidin-4-ol
25 and TFA/DCM 1/9. After purification and freeze drying the titled compound was obtained as a white amorphous solid (33 mg).

¹H-NMR (Acetone-*d*₆, 300 MHz): δ 7.23 (bs, 1H); 7.22 (d, *J* = 8.2 Hz, 1H); 7.14 (dd, *J* = 8.5, 2.4 Hz, 1H); 6.78 (d, *J* = 8.5 Hz, 1H); 6.61 (d, *J* = 2.0 Hz, 1H); 6.50 (dd, *J* = 8.3, 2.0 Hz, 1H); 4.59-4.47 (m, 1H); 4.15 (dd, *J* = 9.8, 5.1 Hz, 1H); 4.06 (dd, *J* = 9.8, 5.6 Hz, 1H);
30 3.92 (d, *J* = 8.3 Hz, 1H); 3.86-3.74 (bs, 2H); 3.85 (d, *J* = 11.2 Hz, 1H); 3.77 (d, *J* = 8.3 Hz,

1H); 3.66 (d, $J = 11.2$ Hz, 1H); 3.65-3.56 (m, 2H); 3.50 (d, $J = 9.0$ Hz, 1H); 3.55-3.40 (m, 2H); 3.46 (d, $J = 9.0$ Hz, 1H); 3.16 (bs, 2H); 2.48-2.14 (m, 4H); 1.48 (s, 3H)
APCI-MS: m/z 519(MH^+)

5 **Example 94**

(4*R*)-2-(2-([(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-hydroxybenzoyl)-4-methylisoxazolidin-4-ol trifluoroacetate (salt)

10 **Step I:**

2-[[[(2*R*)-2-Methyloxiranyl]methoxy]-1*H*-isoindole-1,3(2*H*)-dione

Prepared from N-hydroxyphthalimide and [(2*R*)-2-methyloxiran-2-yl]methyl 3-nitrobenzenesulfonate (Chen, J.; Shum, W., *Tetrahedron Letters*, **1993**, 34(48), 7663-6) by the method of Example 93 Step I.

15 1H -NMR ($CDCl_3$; 400 MHz): δ 1.63 (3H, s), 2.69 (1H, d), 2.76 (1H, d), 4.17 (1H, d), 4.21 (1H, d), 7.73-7.78 (2H, m), 7.82-7.87 (2H, m)
MS (APCI) 234 [$M+H$] $^+$

Step II:

20 2-[[[(2*R*)-3-Chloro-2-hydroxy-2-methylpropyl]oxy]-1*H*-isoindole-1,3(2*H*)-dione

Prepared from 2-[[[(2*R*)-2-Methyloxiranyl]methoxy]-1*H*-isoindole-1,3(2*H*)-dione by the method of Example 93 Step II.

1H -NMR ($CDCl_3$; 400 MHz): δ 1.29(3H, s), 3.67 (1H, d), 3.76 (1H, d), 4.09 (1H, d), 4.15 (1H, d), 7.86 (4H, s), 5.24 (1H, s)

25

Step III:

2-[[[(4*R*)-4-Hydroxy-4-methyl-2-isoxazolidinyl]carbonyl]- benzoic acid methyl ester

Prepared from 2-[[[(2*R*)-3-Chloro-2-hydroxy-2-methylpropyl]oxy]-1*H*-isoindole-1,3(2*H*)-dione by the method of Example 93 Step III.

¹H-NMR (CDCl₃; 400 MHz): δ 1.52 (3H, s), 3.59 (1H, d), 3.81 (1H, d), 3.88 (1H, d), 4.04 (1H, s), 4.34 (1H, d), 3.92 (3H, s), 7.45 (1H, d), 7.49 (1H, t), 7.62 (1H, t), 8.00 (1H, d)

Step IV:

(4*R*)-4-Methyl-4-isoxazolidinol hydrochloride

Prepared from 2-[[*(4R)*-4-Hydroxy-4-methyl-2-isoxazolidinyl]carbonyl]- benzoic acid methyl ester by the method of Example 93 Step IV.

¹H-NMR (CDCl₃; 400 MHz): δ 1.42 (3H, s), 3.29 (1H, d), 3.41 (1H, dD), 3.87 (1H, d), 4.05 (1H, dd)

Step V:

(4*R*)-2-{2-[[*(2S)*-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoyl}-4-methylisoxazolidin-4-ol

The subtitled compound was prepared analogous to the compound Example 91 Step III

from 2-[[*(2S)*-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoic acid (118 mg, 0.2 mmol) and (*4R*)-4-methyl-4-isoxazolidinol hydrochloride (28 mg, 0.2 mmol).

APCI-MS: m/z 639 (MH⁺)

Step VI:

(4*R*)-2-(2-[[*(2S)*-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)-4-methylisoxazolidin-4-ol trifluoroacetate (salt)

The titled compound was prepared analogous to the compound Example 91 Step IV from

(*4R*)-2-{2-[[*(2S)*-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoyl}-4-methylisoxazolidin-4-ol and TFA/DCM 1/9. After purification and freeze drying the titled compound was obtained as a white amorphous solid (30 mg).

¹H-NMR (Acetone-*d*₆, 300 MHz): δ 7.23 (bs, 1H); 7.22 (d, *J* = 8.2 Hz, 1H); 7.14 (dd, *J* = 8.5, 2.4 Hz, 1H); 6.78 (d, *J* = 8.5 Hz, 1H); 6.61 (d, *J* = 2.0 Hz, 1H); 6.50 (dd, *J* = 8.3, 2.0

Hz, 1H); 4.60-4.48 (m, 1H); 4.15 (dd, $J = 9.5, 4.5$ Hz, 1H); 4.03 (dd, $J = 9.5, 6.3$ Hz, 1H); 3.92 (d, $J = 8.4$ Hz, 1H); 3.87-3.72 (bs, 2H); 3.82 (d, $J = 10.9$ Hz, 1H); 3.75 (d, $J = 8.4$ Hz, 1H); 3.69 (d, $J = 10.9$ Hz, 1H); 3.66 (bs, 1H); 3.56-3.38 (m, 2H); 3.42 (dd, $J = 8.8, 13.5$ Hz, 1H); 3.17 (bs, 2H); 2.48-2.14 (m, 4H); 1.48 (s, 3H)

5 APCI-MS: m/z 519 (MH^+)

Example 95

2-[[[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-*N*-(methylsulfonyl)benzamide trifluoroacetate

10

Step I:

tert-butyl 2-[(2*S*)-oxiran-2-ylmethoxy]benzoate

A mixture of *tert*-butyl salicylate (2.01 g, 10.3 mmol), (2*S*)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (2.69 g, 10.4 mmol) and cesium carbonate (4.05 g, 12.4 mmol) in
15 dimethylformamide (20 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate, Na_2SO_4 , filtered, concentrated in vacuo. The residue was purified by silica gel flash chromatography (ethyl acetate 40%, heptane 60%) and gave the subtitle compound (2.3 g, 89 %).

20 1H -NMR ($CDCl_3$, 400 MHz): δ 7.71 (dd, $J = 1.8, 7.7$ Hz, 1H); 7.41 (dd, $J = 1.8, 7.8$ Hz, 1H); (dd, $J = 0.8, 7.5$ Hz, 1H); 6.98 (d, $J = 8.4$ Hz, 1H); 4.29 (dd, $J = 3.2, 11.0$ Hz, 1H); 4.06 (dd, $J = 5.2, 11.0$ Hz, 1H); 3.42-3.37 (m, 1H); 2.93-2.89 (m, 1H); 2.86-2.83 (m, 1H)
APCI-MS: m/z 251 (MH^+)

25 Step II:

tert-butyl 2-[[[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]benzoate

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (390 mg, 1.6 mmol) and
30 *tert*-butyl 2-[(2*S*)-oxiran-2-ylmethoxy]benzoate (350 mg, 1.6 mmol) in ethanol was heated

at reflux overnight. The volatiles were removed in vacuo, the residue was used without further purification.

APCI-MS: m/z 474 (MH^+)

5 **Step III:**

2-(((2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-[(4-methoxybenzyl)oxy]propyl)oxy)benzoic acid

To a suspension of sodium hydride (170 mg, 4.2 mmol) in THF (10 mL) under argon at 0 °C, was added *tert*-butyl 2-(((2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl)oxy}benzoate (750 mg, 1.6mmol) in THF (10 mL) and 1-
10 (chloromethyl)-4-methoxybenzene (250mg, 1.6mmol) in THF (10 mL). The mixture was stirred at room temperature overnight, poured over ice and pH adjusted to 1 with HCl (aq). It was then extracted with ethyl acetate, the organic layer was dried over sodium sulphate (Na_2SO_4), the volatiles were removed in vacuo. The residue was purified by HPLC
15 (acetonitrile/water, 0.025% ammonium hydroxid) and gave the subtitle compound (91 mg)
APCI-MS: m/z 538 (MH^+)

Step IV:

2-(((2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-[(4-methoxybenzyl)oxy]propyl)oxy)-*N*-(methylsulfonyl)benzamide
20

A mixture of 2-(((2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-[(4-methoxybenzyl)oxy]propyl)oxy)benzoic acid (90 mg, 0.17 mmol), *N,N*-dimethylpyridin-4-amine (22 mg, 0.18 mmol), methanesulfonamide (18 mg, 0.19 mmol) and *N*-[3-
25 (dimethylamino)propyl]-*N'*-ethylcarbodiimide hydrochloride (35 mg, 0.18 mmol) in dichloromethane (5 mL) was stirred under argon at room temperature overnight. The mixture was poured in 1M HCl (aq), the two layers were separated, the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulphate, the volatiles were removed in vacuo, the residue (117 mg) was used without
30 further purification.

APCI-MS: m/z 615 (MH^+)

Step V:

2- $\{[(2S)$ -3-(5-chloro-1' H ,3' H -spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ - N -(methylsulfonyl)benzamide

2- $\{[(2S)$ -3-(5-chloro-1' H ,3' H -spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-[(4-methoxybenzyl)oxy]propyl]oxy $\}$ - N -(methylsulfonyl)benzamide (104 mg, 0.17 mmol) was stirred in a mixture of trifluoroacetic acid (500 μ L) and dichloromethane (3 mL), at room temperature for 1 hour. The volatiles were removed in vacuo, the residue was purified by HPLC (acetonitrile/water, 0.025% ammonium hydroxid) and gave the subtitle compound (31 mg, overall yield Steps II-V 3.9 %).

1H -NMR (acetone- d_6 , 400 MHz): δ 7.92 (dd, J = 1.8, 7.8 Hz, 1H); 7.62 (dd, J = 1.8, 8.3 Hz, 1H); 7.28-7.22 (m, 2H); 7.19-7.11 (m, 2H); 6.77 (d, J = 8.5 Hz, 1H); 4.76-4.69 (m, 1H); 4.42-4.32 (m, 2H); 3.98-3.44 (m, 6H); 3.42 (s, 3H); 3.19 (br.s, 2H); 2.41-2.19 (m, 4H)
APCI-MS: m/z 495 (MH^+)

Step VI:

2- $\{[(2S)$ -3-(5-chloro-1' H ,3' H -spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ - N -(methylsulfonyl)benzamide trifluoroacetate

2- $\{[(2S)$ -3-(5-chloro-1' H ,3' H -spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ - N -(methylsulfonyl)benzamide (31 mg, 0.06 mmol) was dissolved in dichloromethane, trifluoroacetic acid (100 μ L) was added. Volatiles were removed in vacuo and the subtitle compound (35 mg) was obtained.

APCI-MS: m/z 495 (MH^+)

Example 96

2- $\{[(2S)$ -3-(5-chloro-1' H ,3' H -spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ - N -1' H -tetrazol-5-ylbenzamide bis(trifluoroacetate)

Step 1:

2-[[[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}benzoic acid hydrochloride

- 5 A mixture of *tert*-butyl 2-[[[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}benzoate (200 mg, 0.42 mmol) and conc. aqueous HCl (3 mL) in dichloromethane (25 mL) was stirred at room temperature for 48 hours. Volatiles were removed in vacuo, the brown residue was used without further purification
APCI-MS: *m/z* 418 (MH⁺)

10

Step II:

2-[[[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-1*H*-tetrazol-5-ylbenzamide bis(trifluoroacetate)

- 15 A mixture of 2-[[[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}benzoic acid hydrochloride (110 mg, 0.24 mmol), 1*H*-tetrazol-5-amine (27 mg, 0.26 mmol) and PS-Carbodiimid (850 mg, 1 mmol) was stirred in dichloromethane (10 ml) at room temperature overnight. Volatiles were removed in vacuo, the residue was purified by HPLC (acetonitrile/water, 0.1% trifluoroacetic acid), and gave the subtitle
20 compound (23 mg, overall yield Steps I-II 11 %).

- ¹H-NMR (acetone-*d*₆, 400 MHz): δ 11.43 (br. s, 1H); 8.03 (dd, *J* = 1.7, 7.8 Hz, 1H); 7.65 (dd, *J* = 1.9, 7.1 Hz, 1H); 7.32 (d, *J* = 8.3 Hz, 1H); 7.25-7.17 (m, 2H); 7.14 (dd, *J* = 2.4, 8.5 Hz, 1H); 6.79 (d, *J* = 8.5 Hz, 1H); 4.85-4.78 (m, 1H); 4.52-4.39 (m, 2H); 3.98-3.76 (m, 2H); 3.75-3.67 (m, 2H); 3.66-3.50 (m, 2H); 3.22 (br. s, 2H); 2.47-2.32 (m, 2H); 2.31-2.20 (m, 2H)

25

APCI-MS: *m/z* 485 (MH⁺)

Example 97

3- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4- $\{[(3R)$ -3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenol bis(trifluoroacetate) (salt)

5 **Step I:**

(2*S*)-1-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-{2- $\{[(3R)$ -3-(dimethylamino)pyrrolidin-1-yl]carbonyl $\}$ -5-[(4-methoxybenzyl)oxy]phenoxy}propan-2-ol

A mixture of PS-carbodiimide (530 mg, 0.68 mmol) and dichloromethane (6 mL) was stirred at room temperature for 15 minutes, a solution of 2- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4-[(4-methoxybenzyl)oxy]benzoic acid hydrochloride (200 mg, 0.32 mmol) in NMP (1 mL) and dichloromethane (2 mL) was added, the mixture was stirred for 30 minutes, a solution of (3*R*)-*N,N*-dimethylpyrrolidin-3-amine (48 mg, 0.42 mmol) in dichloromethane (2 mL) was added. The mixture was stirred at room temperature overnight, filtrated, the filtrate was washed with brine, dried with sodium sulphate. Volatiles were removed in vacuo, the residue was used without further purification

APCI-MS: *m/z* 650 (*MH*⁺)

20 **Step II:**

3- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4- $\{[(3R)$ -3-isopropylpyrrolidin-1-yl]carbonyl}phenol bis(trifluoroacetate)

To a solution of (2*S*)-1-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-{2- $\{[(3R)$ -3-isopropylpyrrolidin-1-yl]carbonyl $\}$ -5-[(4-methoxybenzyl)oxy]phenoxy}propan-2-ol (crude product from the previous step) and dichloromethane (3 mL) was added trifluoroacetic acid (600 μ L). The mixture was stirred at room temperature for 1 h, volatiles were removed in vacuo, the residue was purified by HPLC (acetonitrile/water, 0.1% trifluoroacetic acid) and gave (60 mg, overall yield Steps I-II 25 %) of the subtitle compound.

¹H-NMR (acetone-d₆, 400 MHz): δ 7.22 (s, 1H); 7.15-7.11 (m, 2H); 6.77 (d, *J* = 8.5 Hz, 1H); 6.64-6.60 (m, 1H); 6.53-6.49 (m, 1H); 4.63-4.49 (m, 2H); 4.17-3.96 (m, 4H); 3.96-3.72 (m, 4H); 3.71-3.38 (m, 6H); 3.17 (br. s, 2H); 3.00 (br. s, 3H); 2.94 (br. s, 3H); 2.60-2.18 (m, 6H).

5 APCI-MS: *m/z* 530 (MH⁺)

Example 98

3-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-{{{(3*S*)-3-(dimethylamino)pyrrolidin-1-yl}carbonyl}phenol
10 bis(trifluoroacetate)

The title compound was prepared using (3*S*)-*N,N*-dimethylpyrrolidin-3-amine as described in Example 97.

15 ¹H-NMR (Acetone-*d*₆, 300 MHz): δ 7.25-7.20 (m, 1H); 7.16-7.11 (m, 2H); 6.77 (d, *J* = 8.5 Hz, 1H); 6.63-6.58 (m, 1H); 6.54-6.48 (m, 1H); 4.70-4.52 (m, 1H); 4.20-3.98 (m, 3H); 3.96-3.72 (m, 4H); 3.70-3.36 (m, 6H); 3.17 (bs, 2H); 3.00 (s, 3H); 2.95 (s, 3H); 2.62-2.16 (m, 6H)

APCI-MS: *m/z* 530 (MH⁺)

20 Example 99

(3*S*)-1-(5-chloro-2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)pyrrolidin-3-ol trifluoroacetate

Step I:

25 Methyl 5-chloro-2,4-dihydroxybenzoate

Prepared from methyl 2,4-dihydroxybenzoate using the procedure described by Anderson, W. K., et al., *J. Med. Chem.* 1996, 39, 46 – 55.

¹H-NMR (CDCl₃, 400 MHz): δ 10.85 (s, 1H), 7.84 (s, 1H), 6.63 (s, 1H), 5.99 (s, 1H), 3.95 (s, 3H)

Step II:**Methyl 5-chloro-2-hydroxy-4-[(4-methoxybenzyl)oxy]benzoate**

To a solution of methyl 5-chloro-2,4-dihydroxybenzoate (0.41 g, 2 mmol) in acetone were added 1-(chloromethyl)-4-methoxybenzene (0.32 g, 2 mmol) and K₂CO₃ (0.28 g, 2 mmol).

5 The reaction mixture was heated with reflux for 3 days, then cooled to room temperature. The inorganic material was removed by filtration. The solvent was distilled in vacuo, and the residue was recrystallized from methanol to afford white solid (0.37 g, 60 %).

¹H-NMR (CDCl₃, 400 MHz): δ 10.89 (s, 1H), 7.82 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.56 (s, 1H), 5.09 (s, 2H), 3.92 (s, 3H), 3.82 (s, 3H)

10

Step III:**Methyl 5-chloro-4-[(4-methoxybenzyl)oxy]-2-[(2*S*)-oxiran-2-ylmethoxy]benzoate**

A solution of methyl 5-chloro-2-hydroxy-4-[(4-methoxybenzyl)oxy]benzoate (0.37 g, 1.16 mmol), (2*S*)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (0.30 g, 1.16 mmol) and caesium carbonate (0.45 g, 1.4 mmol) in dimethylformamide (15 mL) was stirred at room temperature overnight. The mixture was partitioned between water and ethyl acetate, and the organic phase was washed twice with water and once with brine, and finally concentrated. The crude material was purified by flash chromatography on silica gel (eluent: ethyl acetate/*n*-heptane), yielding the titled compound (0.33, 74%).

20 ¹H-NMR (CDCl₃, 400 MHz): δ 7.91 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 2H), 6.92 (dd, *J* = 6.7, 2.0 Hz, 2H), 6.66 (s, 1H), 5.14 (m, 2H), 4.33 (dd, *J* = 11.4, 2.6 Hz, 1H), 3.98 (dd, *J* = 11.5, 5.1 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.36 (m, 1H), 2.93 - 2.87 (m, 2H)

APCI-MS: *m/z* 379 (MH⁺)

25 **Step IV****Methyl 5-chloro-2-[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoate trifluoroacetate (salt)**

A solution of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (100 mg, 0.45 mmol) and methyl 5-chloro-4-[(4-methoxybenzyl)oxy]-2-[(2*S*)-oxiran-2-ylmethoxy]benzoate (170 mg, 0.45 mmol) in ethanol (5 mL) was refluxed for 6 h. The solvent was distilled off under

30

reduced pressure. The residue was purified by HPLC (eluent: [acetonitrile /water + 0.1 % TFA]) to afford a colourless solid (218 mg, 67 %).

APCI-MS: m/z 602 (MH^+)

5 **Step V:**

5-chloro-2-([(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-[(4-methoxybenzyl)oxy]benzoic acid hydrochloride

To a mixture of methyl 5-chloro-2-([(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-[(4-methoxybenzyl)oxy]benzoate

10 trifluoroacetate (220 mg, 0.3 mmol) in ethanol (10 mL) was added a solution of potassium hydroxide (4 g) and water (4 mL). The mixture was stirred at room temperature for 3 hours, pH was adjusted to 1 with aqueous HCl (37 %), extracted with ethyl acetate, dried with sodium sulphate. Volatiles was removed in vacuo, the subtitle compound (180 mg) required no further purification.

15 APCI-MS: m/z 588 (MH^+)

Step VI:

(3*S*)-1-{5-chloro-2-([(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-[(4-methoxybenzyl)oxy]benzoyl}pyrrolidin-3-ol

20 **trifluoroacetate**

A mixture of PS-carbodiimide (250 mg, 0.32 mmol) and dichloromethane (3 mL) was stirred at room temperature for 15 minutes, a solution of 5-chloro-2-([(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-[(4-methoxybenzyl)oxy]benzoic acid hydrochloride (100 mg, 0.16 mmol) in NMP (0.5 mL) and dichloromethane (1 mL) was added, the mixture was stirred for 30 minutes, a solution of (3*S*)-pyrrolidin-3-ol (18 mg, 0.21 mmol) in dichloromethane (1 mL) was added. The mixture was stirred at room temperature overnight, filtrated, the filtrate was washed with brine, dried with sodium sulphate. Volatiles were removed in vacuo, the residue was purified by HPLC (acetonitrile/water, 0.1 % trifluoroacetic acid), and gave (45 mg) of the subtitle compound.

30

APCI-MS: m/z 657 (MH^+)

Step VII:

(3*S*)-1-(5-chloro-2-{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)pyrrolidin-3-ol trifluoroacetate

To a solution of (3*S*)-1-{5-chloro-2-{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoyl}pyrrolidin-3-ol trifluoroacetate (45 mg, 0.05 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (0.3 mL). The mixture was stirred at room temperature for 20 minutes, volatiles was removed in vacuo. The residue was purified by HPLC (acetonitrile/water, 0.1 % trifluoroacetic acid), and gave (22 mg, overall yield Steps V-VII 11 %) of the subtitle compound.

1H -NMR (acetone- d_6 , 400 MHz): δ 7.24-7.22 (m, 2H); 7.13 (d, J = 8.4 Hz, 1H); 6.87 (d, J = 13.7 Hz, 1H); 6.77 (d, J = 8.5 Hz, 1H); 4.56-4.46 (m, 2H); 4.44-4.39 (m, 1H); 4.17-4.02 (m, 2H); 3.87-3.72 (m, 2H); 3.70-3.60 (m, 2H); 3.60-3.26 (m, 7H); 3.16 (br. s, 2H); 2.45-2.16 (m, 4H); 2.03-1.80 (m, 2H).

APCI-MS: m/z 537 (MH^+)

Example 100

3-{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-{[(3*S*)-3-methoxypyrrolidin-1-yl]carbonyl}phenol trifluoroacetate

Step I:

(2*S*)-1-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-(5-[(4-methoxybenzyl)oxy]-2-{[(3*S*)-3-methoxypyrrolidin-1-yl]carbonyl}phenoxy)propan-2-ol

A mixture of PS-carbodiimide (277 mg, 0.35 mmol) and dichloromethane (3 mL) was stirred at room temperature for 15 minutes, a solution of 2-{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-

methoxybenzyl)oxy]benzoic acid hydrochloride (100 mg, 0.16 mmol) in NMP (0.5 mL) and dichloromethane (1 mL) was added, the mixture was stirred for 30 minutes, a solution of (3*S*)-3-methoxypyrrolidine (27 mg, 0.27 mmol) in dichloromethane (1 mL) was added. The mixture was stirred at room temperature overnight, filtrated, the filtrate was washed
5 with brine, dried with sodium sulphate. Volatiles were removed in vacuo, the residue was purified by HPLC (acetonitrile/water, 0.025% ammonium hydroxid) and gave (35 mg) of the subtitle compound.

APCI-MS: m/z 637 (MH^+)

10 **Step II:**

3-{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-{[(3*S*)-3-methoxypyrrolidin-1-yl]carbonyl}phenol trifluoroacetate

15 To a solution of (2*S*)-1-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-(5-[(4-methoxybenzyl)oxy]-2-{[(3*S*)-3-methoxypyrrolidin-1-yl]carbonyl}phenoxy)propan-2-ol (35 mg, 0.05 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (0.3 mL). The mixture was stirred at room temperature for 2 hours, volatiles were removed and the residue was purified by HPLC (acetonitrile/water, 0.1 % trifluoroacetic acid) and gave 25
20 mg (overall yield Steps I-II 25 %) of the title compound.

¹H-NMR (acetone-*d*₆, 400 MHz): δ 7.23 (s, 1H); 7.16-7.10 (m, 2H); 6.77 (d, J = 8.7 Hz, 1H); 6.64-6.61 (m, 1H); 6.52 (dd, J = 2.1, 8.2 Hz, 1H); 4.54-4.45 (m, 1H); 4.17-3.95 (m, 3H); 3.88-3.70 (m, 2H); 3.69-3.60 (m, 2H); 3.60-3.42 (m, 4H); 3.40-3.31 (m, 3H); 3.26 (s, 2H); 3.17 (br. s, 2H); 2.46-2.17 (m, 4H); 2.10-1.92 (m, 2H).

25 APCI-MS: m/z 517 (MH^+)

Example 101

3-{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-{[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenol trifluoroacetate
30

Step I:

(2*S*)-1-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-{2-[[*(2R)*-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl]-5-[(4-methoxybenzyl)oxy]phenoxy}propan-2-ol

A mixture of PS-carbodiimide (280 mg, 0.36 mmol) and dichloromethane (2.5 mL) was stirred at room temperature for 15 minutes, a solution of 2-[[*(2S)*-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoic acid hydrochloride (100 mg, 0.16 mmol) in NMP (0.6 mL) and dichloromethane (1 mL) was added, the mixture was stirred for 30 minutes, a solution of *(2R)*-pyrrolidin-2-ylmethanol (30 mg, 0.30 mmol) in dichloromethane (1 mL) was added. The mixture was stirred at room temperature overnight and filtered. Volatiles were removed in vacuo, the residue was purified by HPLC (acetonitrile/water, 0.025% ammonium hydroxid) and gave (51 mg) of the subtitle compound.

APCI-MS: m/z 637 (MH^+)

Step II:

3-[[*(2S)*-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[[*(2R)*-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl]phenol trifluoroacetate

To a solution of *(2S)*-1-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-{2-[[*(2R)*-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl]-5-[(4-methoxybenzyl)oxy]phenoxy}propan-2-ol (51 mg, 0.08 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (0.3 mL). The mixture was stirred at room temperature for 30 minutes, volatiles were removed, the residue was purified by HPLC (acetonitrile/water, 0.1 % trifluoroacetic acid) and gave 20 mg (overall yield Steps I-II 20 %) of the title compound.

1H -NMR (acetone- d_6 , 400 MHz): δ 7.23 (s, 1H); 7.15-7.10 (m, 2H); 6.77 (d, J = 8.6 Hz, 1H); 6.60-6.57 (m, 1H); 6.50 (dd, J = 2.1, 8.2 Hz, 1H); 4.58-4.48 (m, 1H), 4.32-4.24 (m,

1H); 4.14-4.06 (m, 2H); 3.90-3.60 (m, 4H); 3.60-3.40 (m, 4H); 3.32-3.20 (m, 2H); 3.16 (br. s, 2H); 2.46-2.16 (m, 4H); 1.95-1.66 (m, 2H); 1.35-1.29 (m, 2H).

APCI-MS: m/z 517 (MH⁺)

5 **Example 102**

3-([(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-([(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl)phenol trifluoroacetate

The title compound was prepared as described in Example 101 using (2*R*)-pyrrolidin-2-ylmethanol.

¹H-NMR (acetone-d₆, 400 MHz): δ 7.23 (s, 1H); 7.16-7.05 (m, 2H); 6.77 (d, *J* = 8.5 Hz, 1H); 6.64-6.57 (m, 1H); 6.50 (dd, *J* = 2.2, 8.4 Hz, 1H); 4.60-4.51 (m, 1H), 4.30-4.22 (m, 1H); 4.14-4.10 (m, 2H); 3.90-3.72 (m, 2H); 3.70-3.24 (m, 8H); 3.17 (br. s, 2H); 2.44-2.14 (m, 4H); 1.92-1.68 (m, 4H).

15 APCI-MS: m/z 517 (MH⁺)

Example 103

3-([(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-{[3-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenol trifluoroacetate

20 The title compound was prepared as described in Example 101 pyrrolidin-3-ylmethanol hydrochloride .

¹H-NMR (acetone-d₆, 400 MHz): δ 7.23 (s, 1H); 7.16-7.08 (m, 2H); 6.80-6.75 (m, 1H); 6.67-6.62 (m, 1H); 6.53-6.48 (m, 1H); 4.52-4.44 (m, 1H), 4.17-4.02 (m, 2H); 3.90-3.10 (m, 15H); 2.50-2.16 (m, 4H); 2.02-1.68 (m, 2H).

APCI-MS: m/z 517 (MH⁺)

Example 104

1-(2-([(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-hydroxybenzoyl)-D-prolinamide trifluoroacetate

Step I:

1-{2-[[[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoyl]-D-prolinamide

5 A mixture of PS-carbodiimide (280 mg, 0.36 mmol) and dichloromethane (2.5 mL) was stirred at room temperature for 15 minutes, a solution of 2-[[[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoic acid hydrochloride (100 mg, 0.16 mmol) in NMP (0.6 mL) and dichloromethane (1 mL) was added, the mixture was stirred for 30 minutes, a solution
10 of D-prolinamide (29 mg, 0.25 mmol) in dichloromethane (1 mL) was added. The mixture was stirred at room temperature overnight and filtrated. Volatiles were removed in vacuo, the residue was purified by HPLC (acetonitrile/water, 0.025% ammonium hydroxid) and gave (68 mg) of the subtitle compound.

APCI-MS: m/z 650 (MH^+)

15

Step II:

1-(2-[[[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl]-D-prolinamide trifluoroacetate

20 To a solution of 1-(2-[[[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoyl]-D-prolinamide (68 mg, 0.10 mmol) in dichloromethane was added trifluoroacetic acid (0.3 mL). The mixture was stirred at room temperature for 30 minutes, volatiles were removed, the residue was purified by HPLC (acetonitrile/water, 0.1 % trifluoroacetic acid) and gave 28 mg (overall yield
25 Steps I-II 27 %) of the title compound.

¹H-NMR (acetone-*d*₆, 400 MHz, 2 rotamers): δ 7.23 (s, 1H); 7.22-7.16 and 6.64-6.54 (m, 3H); 7.15-7.10 and 7.06-7.02 (m, 2H); 6.77 (d, $J = 8.4$ Hz, 1H); 6.53-6.48 and 6.46-6.41 (m, 1H); 4.62-4.47 (m, 2H); 4.16-4.02 (m, 2H); 3.92-3.42 (m, 8H); 3.34-3.22 (m, 2H); 3.16 (br. s, 2H); 2.46-2.14 (m, 4H); 2.12-1.76 (m, 2H).

30 APCI-MS: m/z 530 (MH^+)

Example 105

N-(4-hydroxy-2-{[(2S)-2-hydroxy-3-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide trifluoroacetate (salt)

5

The title compound was prepared from 3*H*-spiro[1-benzofuran-2,4'-piperidine] as described in Example 27.

¹H-NMR (acetone-d₆, 400 MHz): δ 8.52 (s, 1H), 7.93 (d, *J* = 8.7 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 6.86 (t, *J* = 7.3 Hz, 1H), 6.75 (d, *J* = 7.9 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 6.40 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.53 (m, 1H), 4.08 (m, 2H), 3.94 - 3.39 (m, 6H), 3.15 (s, 2H), 2.45 - 2.15 (m, 4H), 2.09 (s, 3H)
APCI-MS: *m/z* 413 (MH⁺).

Example 106

15 **N-(4-hydroxy-2-{[(2S)-2-hydroxy-3-(5-methyl-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide trifluoroacetate (salt)**

The title compound was prepared from 5-Methyl-3*H*-spiro[1-benzofuran-2,4'-piperidine] as described in Example 27.

20 ¹H-NMR (acetone-d₆, 400 MHz): δ 8.56 (s, 1H), 7.90 (d, *J* = 8.7 Hz, 1H), 7.01 (s, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.63 (d, *J* = 8.1 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 6.41 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.52 (s, 1H), 4.07 (d, *J* = 3.8 Hz, 2H), 3.92 - 3.38 (m, 6H), 3.09 (s, 2H), 2.42 - 2.13 (m, 4H), 2.24 (s, 3H), 2.10 (s, 3H)
APCI-MS: *m/z* 427 (MH⁺).

25

Example 107

N-(5-chloro-2-{[(2S)-2-hydroxy-3-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide trifluoroacetate (salt)

The title compound was prepared from 3*H*-spiro[1-benzofuran-2,4'-piperidine] as described in Example 83.

¹H-NMR (DMSO-*d*₆, 400 MHz): δ 9.61 (br. s, 1H), 9.02 (m, 1H), 7.91 (s, 1H), 7.21 (d, *J* = 7.3 Hz, 1H), 7.11 (m, 1H), 6.85 (m, 2H), 6.77 (d, *J* = 7.9 Hz, 1H), 4.38 (m, 1H), 4.06 (m, 2H), 3.85 (s, 3H), 3.66 - 3.12 (m, 6H), 3.08 (s, 2H), 2.23 - 1.94 (m, 7H)
APCI-MS: *m/z* 461 (MH⁺).

Example 108

N-(5-chloro-4-hydroxy-2-(((2*S*)-2-hydroxy-3-(1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl)oxy}phenyl)acetamide trifluoroacetate (salt)

To a stirred solution of N-(5-chloro-2-(((2*S*)-2-hydroxy-3-(1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl)oxy}-4-methoxyphenyl)acetamide trifluoroacetate (116 mg, 0.2 mmol) in dichloromethane (50 ml) at 0 °C was added a solution of BBr₃ (1 M in dichloromethane, 2 ml, 2 mmol) under argon. The stirring was continued at 0 °C for 6 h, then the reaction mixture was quenched with methanol. The solvent was removed in vacuo, the residue purified by HPLC (eluent: [acetonitrile / water + 0.1 % TFA]) to afford colourless solid (12 mg, 10 %).

¹H-NMR (acetone-*d*₆, 400 MHz): δ 8.62 (s, 1H), 8.26 (s, 1H), 7.21 (d, *J* = 7.3 Hz, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 6.86 (t, *J* = 7.4 Hz, 1H), 6.75 (m, 2H), 4.55 (m, 1H), 4.10 (m, 2H), 3.93 - 3.19 (m, 8H), 3.16 (s, 2H), 2.43 - 2.15 (m, 4H), 2.11 (s, 3H)
APCI-MS: *m/z* 447 (MH⁺).

Example 109

(3*S*)-N-(2-(((2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl)oxy}-4-methoxyphenyl)-3-hydroxypyrrolidine-1-carboxamide trifluoroacetate (salt)

The title compound was prepared using 6-methoxy-1,3-benzoxazol-2(3*H*)-one as described in Example 84.

¹H-NMR (acetone-d₆, 400 MHz): δ 7.74 (m, 1H), 7.23 (s, 1H), 7.13 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.03 (s, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.61 (d, *J* = 2.7 Hz, 1H), 6.49 (dd, *J* = 8.8, 2.7 Hz, 1H), 4.59 (m, 1H), 4.47 (m, 1H), 4.14 (m, 2H), 3.80 (m, 2H), 3.75 (s, 3H), 3.64 - 3.40 (m, 8H), 3.16 (s, 2H), 2.44 - 2.16 (m, 4H), 2.09 - 1.89 (m, 2H)

5 APCI-MS: *m/z* 532 (MH⁺).

Example 110

(3S)-N-(2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxyphenyl)-3-hydroxypyrrolidine-1-carboxamide
10 trifluoroacetate (salt)

To a stirred solution of (3S)-N-(2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-methoxyphenyl)-3-hydroxypyrrolidine-1-carboxamide trifluoroacetate (59 mg, 0.09 mmol) in dichloromethane (50 ml) at 0 °C was
15 added a solution of BBr₃ (1 M in dichloromethane, 1.8 ml, 1.8 mmol) under argon. The stirring was continued at 0 °C for 4 h, then the reaction mixture was quenched with methanol. The solvent was removed in vacuo, the residue purified by HPLC (eluent: [acetonitrile / water + 0.1 % TFA]) to afford colourless solid (30 mg, 53 %).

¹H-NMR (acetone-d₆, 400 MHz): δ 7.52 (m, 1H), 7.23 (s, 1H), 7.13 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.99 (s, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.57 (d, *J* = 2.5 Hz, 1H), 6.39 (dd, *J* = 8.6, 2.6 Hz, 1H), 4.56 (m, 1H), 4.46 (m, 1H), 4.07 (m, 2H), 3.90 - 3.21 (m, 10H), 3.16 (s, 2H), 2.42 - 2.16 (m, 4H), 2.09 - 1.90 (m, 2H)

20 APCI-MS: *m/z* 518 (MH⁺).

25 Example 111

(3S)-1-(4-hydroxy-2-{{{(2S)-2-hydroxy-3-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}benzoyl)pyrrolidin-3-ol trifluoroacetate (salt)

Step I:

Methyl 2-{{{(2S)-2-hydroxy-3-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}-4-[(4-methoxybenzyl)oxy]benzoate trifluoroacetate (salt)}

A solution of 3H-spiro[1-benzofuran-2,4'-piperidine] (50 mg, 0.26 mmol) and methyl methyl 4-[(4-methoxybenzyl)oxy]-2-[(2S)-oxiran-2-ylmethoxy]benzoate (91 mg, 0.26 mmol) in ethanol (3 mL) was refluxed for 6 h. The solvent was distilled off under reduced pressure. The residue was purified by HPLC (eluent: [acetonitrile /water + 0.1 % TFA]) to afford a colourless solid (103 mg, 61 %).

APCI-MS: m/z 534 (MH⁺)

Step II:

2-{{{(2S)-2-hydroxy-3-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}-4-[(4-methoxybenzyl)oxy]benzoic acid hydrochloride}

To a mixture of methyl 2-{{{(2S)-2-hydroxy-3-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}-4-[(4-methoxybenzyl)oxy]benzoate trifluoroacetate

(103 mg, 0.16 mmol) in ethanol (5 mL) was added 10 N aq. NaOH solution (1 ml) and water (1 ml). The mixture was stirred at room temperature overnight, pH was adjusted to 1 with aqueous HCl (2 M), extracted with ethyl acetate, dried with sodium sulphate.

Volatiles was removed in vacuo to afford the subtitle compound, which was used without purification.

APCI-MS: m/z 520 (MH⁺)

Step III:

(3S)-1-(4-hydroxy-2-{{{(2S)-2-hydroxy-3-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}benzoyl)pyrrolidin-3-ol trifluoroacetate (salt)}

A mixture of PS-carbodiimide (250 mg, 0.32 mmol) and dichloromethane (5 mL) was stirred at room temperature for 15 minutes, then 2-{{{(2S)-2-hydroxy-3-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}-4-[(4-methoxybenzyl)oxy]benzoic acid hydrochloride (89 mg, 0.16 mmol) was added, and the mixture was stirred for 30 minutes.

A solution of (3S)-pyrrolidin-3-ol (14 mg, 0.16 mmol) in dichloromethane (1 mL) was added. The mixture was stirred at room temperature for 24 h, and filtered. Trifluoroacetic

acid (10 % in dichloromethane, 5 ml) was added, and the stirring was continued for 1 h at room temperature. Volatiles were removed in vacuo, the residue was purified by HPLC (acetonitrile/water, 0.1% trifluoroacetic acid) and gave (14 mg, overall yield Steps II-III 15 %) of the title compound.

5 ¹H-NMR (acetone-d₆, 400 MHz): δ 7.20 (d, *J* = 7.2 Hz, 1H), 7.12 (m, 2H), 6.85 (t, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.60 (dd, *J* = 7.4, 2.0 Hz, 1H), 6.51 (dt, *J* = 8.2, 2.4 Hz, 1H), 4.49 (s, 2H), 4.40 (m, 1H), 4.17 - 4.00 (m, 3H), 3.87 - 3.25 (m, 8H), 3.12 (s, 2H), 2.45 - 2.12 (m, 4H), 2.10 - 1.85 (m, 2H)

APCI-MS: *m/z* 469 (MH⁺).

10

Example 112

2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-5-methylbenzoic acid hydrochloride

15 **Step I:**

Methyl 5-methyl-2-[(2*S*)-oxiran-2-ylmethoxy]benzoate

A solution of methyl 2-hydroxy-5-methylbenzoate (0.166 g, 1 mmol), (2*S*)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (0.26 g, 1 mmol) and caesium carbonate (0.39 g, 1.2 mmol) in dimethylformamide (5 mL) was stirred at room temperature overnight. The mixture was partitioned between water and ethyl acetate, and the organic phase was washed twice with water and once with brine, and finally concentrated. The crude material was purified by flash chromatography on silica gel (eluent: ethyl acetate/*n*-heptane), yielding the titled compound (0.16 g, 72%) as colourless oil.

20 ¹H-NMR (CDCl₃, 400 MHz): δ 7.61 (d, *J* = 2.0 Hz, 1H), 7.25 (d, *J* = 9.9 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 4.28 (dd, *J* = 11.2, 3.0 Hz, 1H), 4.07 (dd, *J* = 11.2, 4.9 Hz, 1H), 3.89 (s, 3H), 3.38 (m, 1H), 2.89 (m, 2H), 2.30 (s, 3H)

Step II:

Methyl 2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-5-methylbenzoate trifluoroacetate (salt)

30

A solution of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (112 mg, 0.5 mmol) and methyl 5-methyl-2-[(2*S*)-oxiran-2-ylmethoxy]benzoate (111 mg, 0.5 mmol) in ethanol (5 mL) was refluxed for 6 h. The solvent was distilled off under reduced pressure. The residue was purified by HPLC (eluent: [acetonitrile /water + 0.1 % TFA]) to afford a
5 colourless solid (153 mg, 54 %).

APCI-MS: *m/z* 446 (MH^+)

Step III:

2-{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-
10 hydroxypropyl]oxy}-5-methylbenzoic acid hydrochloride

To a mixture of methyl 2-{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-5-methylbenzoate trifluoroacetate

(153 mg, 0.27 mmol) in ethanol (5 mL) was added 10 N aq. NaOH solution (1 mL) and water (1 mL). The mixture was stirred at room temperature for 3 hours, pH was adjusted to 1
15 with aqueous HCl (2 M), extracted with ethyl acetate, dried with sodium sulphate.

Volatiles was removed in vacuo to afford the subtitle compound (123 mg, 96 %).

¹H-NMR (acetone-*d*₆, 400 MHz): δ 7.68 (d, *J* = 2.1 Hz, 1H), 7.36 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.22 (s, 1H), 7.11 (m, 2H), 6.76 (d, *J* = 8.5 Hz, 1H), 4.68 (m, 1H), 4.27 (m, 1H), 4.17 (m, 1H), 3.72 (br. s, 2H), 3.67 (d, *J* = 13.7 Hz, 1H), 3.51 (br. s, 2H), 3.43 (dd, *J* = 13.5, 8.8 Hz,
20 1H), 3.19 (s, 2H), 2.47 (br. s, 2H), 2.30 (s, 3H), 2.22 (br. s, 2H)

APCI-MS: *m/z* 423 (MH^+)

Example 113

2-{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-
25 hydroxypropyl]oxy}-4-methoxybenzoic acid hydrochloride

The title compounds was prepared using methyl 2-hydroxy-4-methoxybenzoate as described in Example 112.

¹H-NMR (acetone-*d*₆, 400 MHz): δ 7.89 (d, *J* = 8.8 Hz, 1H), 7.23 (m, 1H), 7.12 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.76 (d, *J* = 8.6 Hz, 2H), 6.74 (d, *J* = 2.3 Hz, 2H), 6.65 (dd, *J* = 8.8, 2.3
30

Hz, 1H), 4.70 (m, 1H), 4.31 (m, 1H), 4.22 (m, 1H), 3.89 (s, 3H), 3.73 (br. s, 2H), 3.67 (dd, $J = 13.4, 1.9$ Hz, 1H), 3.58 - 3.45 (m, 2H), 3.41 (dd, $J = 13.5, 8.7$ Hz, 1H), 3.19 (s, 2H), 2.49 (m, 2H), 2.24 (br. d, $J = 14.0$ Hz, 2H)

APCI-MS: m/z 448 (MH^+)

5

Example 114

(3S)-1-(2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-5-methylbenzoyl}pyrrolidin-3-ol trifluoroacetate (salt)

10 A mixture of PS-carbodiimide (78 mg, 0.1 mmol) and dichloromethane (5 mL) was stirred at room temperature for 15 minutes, then 2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-5-methylbenzoic acid hydrochloride (23 mg, 0.05 mmol) was added, and the mixture was stirred for 30 minutes. A solution of (3S)-pyrrolidin-3-ol (5 mg, 0.05 mmol) in dichloromethane (1 mL) was added. The mixture was
15 stirred at room temperature for 24 h, and filtered. Volatiles were removed in vacuo, the residue was purified by HPLC (acetonitrile/water, 0.1% trifluoroacetic acid) and gave (6 mg, 21 %) of the title compound.

1H -NMR (acetone- d_6 , 400 MHz): δ 7.17 (s, 2H), 7.08 (d, $J = 8.5$ Hz, 2H), 7.04 (d, $J = 1.6$ Hz, 2H), 6.99 (dd, $J = 8.3, 5.3$ Hz, 2H), 6.70 (d, $J = 8.4$ Hz, 1H), 4.49 (m, 1H), 4.39 (m,
20 1H), 4.15 (m, 2H), 3.98 (m, 3H), 3.63 (dd, $J = 9.1, 5.4$ Hz, 2H), 3.59 - 3.40 (m, 3H), 3.28 (m, 2H), 3.04 (s, 3H), 2.75 - 2.49 (m, 4H), 2.27 (d, $J = 2.2$ Hz, 4H)

APCI-MS: m/z 501 (MH^+)

Example 115

25 **(3S)-1-(2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-methoxybenzoyl}pyrrolidin-3-ol trifluoroacetate (salt)**

The title compound prepared from 2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-methoxybenzoic acid hydrochloride as described
30 in Example 114.

¹H-NMR (acetone-d₆, 400 MHz): δ 7.23 (s, 1H), 7.19 (dd, *J* = 8.4, 3.1 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.67 (t, *J* = 2.4 Hz, 1H), 6.60 (dt, *J* = 8.4, 2.2 Hz, 1H), 4.51 (m, 2H), 4.39 (m, 1H), 4.22 - 4.12 (m, 2H), 4.08 (m, 1H), 3.83 (s, 3H), 3.85 - 3.25 (m, 8H), 3.16 (s, 2H), 2.35 (br. s, 2H), 2.21 (br. s, 2H)

5 APCI-MS: *m/z* 517 (MH⁺)

Example 116

5-chloro-2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}benzoic acid hydrochloride

10 The title compounds was prepared using methyl 5-chloro-2-hydroxybenzoate as described in Example 112.

¹H-NMR (acetone-d₆, 400 MHz): δ 7.81 (d, *J* = 2.8 Hz, 1H), 7.57 (dd, *J* = 9.0, 2.8 Hz, 1H), 7.26 (d, *J* = 9.0 Hz, 1H), 7.23 (s, 1H), 7.13 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 4.66 (m, 2H), 4.32 (m, 1H), 4.19 (m, 1H), 3.73 (br. s, 2H), 3.69 (d, *J* = 13.3 Hz, 1H),
15 3.54 (br. s, 2H), 3.45 (dd, *J* = 13.5, 8.9 Hz, 1H), 3.20 (s, 2H), 2.46 (br. s, 2H), 2.24 (br. d, *J* = 12.3 Hz, 2H)

APCI-MS: *m/z* 452 (MH⁺)

Example 117

20 **(3S)-1-(5-chloro-2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}benzoyl)pyrrolidin-3-ol trifluoroacetate (salt)**

The title compound prepared from 5-chloro-2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}benzoic acid hydrochloride as
25 described in Example 114.

¹H-NMR (acetone-d₆, 400 MHz): δ 7.39 (dt, *J* = 8.8, 2.4 Hz, 1H), 7.25 (dd, *J* = 4.1, 2.8 Hz, 1H), 7.23 (s, 1H), 7.15 (d, *J* = 8.7 Hz, 1H), 7.12 (s, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 4.53 (m, 2H), 4.42 (m, 1H), 4.23 - 4.06 (m, 3H), 3.76 - 3.14 (m, 12H), 2.33 (br. s, 2H), 2.23 (br. s, 2H)

30 APCI-MS: *m/z* 521 (MH⁺)

Example 118

2-[[[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-5-fluorobenzoic acid hydrochloride

5

The title compounds was prepared using methyl 5-fluoro-2-hydroxybenzoate as described in Example 112.

¹H-NMR (acetone-d₆, 400 MHz): δ 7.56 (dd, *J* = 8.9, 3.2 Hz, 1H), 7.35 (m, 1H), 7.27 (dd, *J* = 9.2, 4.4 Hz, 1H), 7.13 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 4.68 (m, 1H),
10 4.29 (m, 1H), 4.18 (m, 1H), 3.72 (br. s, 2H), 3.68 (br. d, *J* = 13.1 Hz, 3H), 3.51 (br. s, 1H), 3.41 (dd, *J* = 13.4, 9.0 Hz, 3H), 3.19 (s, 2H), 2.53 (br. s, 2H), 2.22 (br. s, 2H)

APCI-MS: *m/z* 436 (MH⁺)

Example 119

15 **(3S)-1-(2-[[[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-5-fluorobenzoyl]pyrrolidin-3-ol trifluoroacetate (salt)**

The title compound prepared from 5-fluoro-2-[[[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]benzoic acid hydrochloride as
20 described in Example 114.

¹H-NMR (acetone-d₆, 400 MHz): δ 7.23 (s, 1H), 7.16 (m, 2H), 7.12 (s, 1H), 7.04 (m, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 4.51 (m, 2H), 4.41 (m, 1H), 4.19 - 4.04 (m, 3H), 3.70 - 3.13 (m, 12H), 2.32 (br. s, 2H), 2.23 (br. s, 2H)

APCI-MS: *m/z* 505 (MH⁺)

25

Example 120

N-(2-[[[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]phenyl]pyrrolidine-1-carboxamide trifluoroacetate (salt)

The title compound was prepared using 1,3-benzoxazol-2(3*H*)-one and pyrrolidine as described in Example 84.

¹H-NMR (acetone-d₆, 400 MHz): δ 8.14 (m, 1H), 7.23 (s, 2H), 7.13 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.99 (m, 1H), 6.90 (m, 2H), 6.76 (d, *J* = 8.6 Hz, 1H), 4.64 (m, 1H), 4.13 (m, 1H), 3.82 (br. s, 2H), 3.61 (br. d, *J* = 13.1 Hz, 2H), 3.55 - 3.42 (m, 8H), 3.18 (s, 2H), 2.35 (br. s, 2H), 2.25 (br. s, 2H), 1.93 (m, 4H)
APCI-MS: *m/z* 486 (MH⁺).

Example 121

Methyl 4-(acetylamino)-3-[[[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]benzoate trifluoroacetate (salt)

Step I:

Methyl 4-(acetylamino)-3-hydroxybenzoate

A solution of methyl 3-hydroxy-4-nitrobenzoate (0.78 g, 3.96 mmol) in THF (40 ml) with Pd on charcoal (10 %, 0.15 g) was stirred in the atmosphere of hydrogen at atmospheric pressure overnight. The mixture was filtered through celite. The solvent was removed in vacuo. The residue was taken into water (20 ml), and acetic anhydride (0.5 ml, 5.29mmol) was added. The mixture was vigorously stirred at 65 °C for 30 min. After cooling to room temperature, the precipitate was collected by filtration, washed with water, and dried. White powder (0.64 g, 77%).

Step II:

Methyl 4-(acetylamino)-3-[(2*S*)-oxiran-2-ylmethoxy]benzoate

A solution of methyl 4-(acetylamino)-3-hydroxybenzoate (0.209 g, 1 mmol), (2*S*)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (0.26 g, 1 mmol) and caesium carbonate (0.39 g, 1.2 mmol) in dimethylformamide (5 mL) was stirred at room temperature overnight. The mixture was partitioned between water and ethyl acetate, and the organic phase was washed twice with water and once with brine, and finally concentrated. The crude material

was purified by flash chromatography on silica gel (eluent: ethyl acetate/n-heptane), yielding the subtitle compound (96 mg, 36%) as colourless oil.

¹H-NMR (CDCl₃, 400 MHz): δ 8.45 (d, *J* = 8.5 Hz, 1H), 8.12 (s, 1H), 7.69 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.54 (d, *J* = 1.7 Hz, 1H), 4.43 (dd, *J* = 11.3, 2.3 Hz, 1H), 3.96 (dd, *J* = 11.3, 6.3 Hz, 1H), 3.89 (s, 3H), 3.41 (m, 1H), 2.96 (t, *J* = 4.5 Hz, 1H), 2.79 (dd, *J* = 4.7, 2.6 Hz, 1H), 2.24 (s, 3H)

APCI-MS: *m/z* 266 (MH⁺).

Step III:

Methyl 4-(acetylamino)-3-([(2*S*)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}benzoate trifluoroacetate (salt)

A solution of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (81 mg, 0.36 mmol) and methyl 4-(acetylamino)-3-[(2*S*)-oxiran-2-ylmethoxy]benzoate (96 mg, 0.36 mmol) in ethanol (5 mL) was refluxed for 5 h. The solvent was distilled off under reduced pressure.

The residue was purified by HPLC (eluent: [acetonitrile /water + 0.1 % TFA]) to afford a colourless solid (177 mg, 82%).

¹H-NMR (acetone-d₆, 400 MHz): δ 8.97 (s, 1H), 8.49 (d, *J* = 8.5 Hz, 1H), 7.64 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.57 (d, *J* = 1.4 Hz, 1H), 7.24 (s, 1H), 7.13 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 4.60 (m, 1H), 4.22 (m, 2H), 3.93 - 3.69 (m, 6H), 3.85 (s, 3H), 3.21 (s, 2H), 2.44 - 2.22 (m, 4H), 2.20 (s, 3H)

APCI-MS: *m/z* 489 (MH⁺).

Example 122

4-(acetylamino)-3-([(2*S*)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}benzoic acid trifluoroacetate (salt)

To a stirred solution of methyl 4-(acetylamino)-3-([(2*S*)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}benzoate trifluoroacetate salt (175 mg, 0.29 mmol) in ethanol (4 ml) was added 2 M aq. NaOH (4 ml). The reaction mixture was stirred at room temperature overnight. Then pH was adjusted to 5 by addition of TFA.

The mixture was concentrated in vacuo and purified by HPLC (eluent: [acetonitrile / water + 0.1 % TFA]) to afford colourless solid (114 mg, 67 %).

¹H-NMR (acetone-d₆, 400 MHz): δ 8.96 (s, 1H), 8.48 (d, *J* = 8.4 Hz, 1H), 7.67 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.58 (d, *J* = 1.1 Hz, 1H), 7.24 (s, 1H), 7.13 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 4.61 (m, 1H), 4.23 (m, 2H), 3.96 - 3.42 (m, 6H), 3.21 (s, 2H), 2.48 - 2.21 (m, 4H), 2.20 (s, 3H)

APCI-MS: *m/z* 475 (MH⁺).

Example 123

N-(2-{[(2*S*)-3-(5-chloro-3'-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)acetamide

The title compound was prepared as described in Example 27 from 5-chloro-3'-fluoro-3*H*-spiro(1-benzofuran-2,4'-piperidine) (57.3 mg, 0.212 mmol) and 4-{(acetylamino)-3-(2*S*)-oxiran-2-ylmethoxy]phenyl acetate (51.2 mg, 0.216 mmol) and to give 18 mg (18%) of the title compound.

APCI-MS: *m/z* 465 (M+H)⁺

Example 124

2-{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-(2-hydroxypropyl)benzamide

Resin-bound carbodiimide (60 mg, 0.08 mmol) was allowed to swell in dichloromethane (0.5 mL) for 30 minutes. 2-{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoic acid (24.7 mg, 0.045 mmol, 0.3 M in 1-methyl-2-pyrrolidinone) was added and after additionally 30 minutes 1-aminopropan-2-ol (0.21 ml, 0.3 M in 1-methyl-2-pyrrolidinone) was added. After reaction over night at room temperature the resin was filtered off, and washed with several portions of dichloromethane. The organic layers were combined and evaporated. The crude material of 2-{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-

hydroxypropyl]oxy}-N-(2-hydroxypropyl)-4-[(4-methoxybenzyl)oxy]benzamide was dissolved in trifluoroacetic acid/dichloromethane (1.2 mL 70/30) and stirred over night at room temperature. The solvents were evaporated and the resulting crude material was purified on C18 with acetonitrile/water 0.1% trifluoroacetic acid as mobile phase. Pure fractions were collected, pooled and evaporated to give the title compound as the trifluoroacetate.

APCI-MS m/z: 490 [MH⁺]

The following compounds in Examples 125 to 166 were prepared by methods analogous to the method described in Example 124.

Example 125

2-{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-N-(2-hydroxy-1,1-dimethylethyl)benzamide

APCI-MS m/z: 505 [MH⁺]

Example 126

2-{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-N-cyclopentyl-4-hydroxybenzamide

APCI-MS m/z: 501 [MH⁺]

Example 127

2-{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-N-(2-methoxyethyl)benzamide

APCI-MS m/z: 491 [MH⁺]

Example 128

2-{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-N-(2-hydroxyphenyl)benzamide

APCI-MS m/z: 525 [MH⁺]

Example 129

N-(tert-butyl)-2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}}-4-hydroxybenzamide

5 APCI-MS m/z: 489 [MH⁺]

Example 130

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}}-4-hydroxy-N-(2-hydroxy-1-methylethyl)benzamide

10 APCI-MS m/z: 491 [MH⁺]

Example 131

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}}-4-hydroxy-N-isobutylbenzamide

15 APCI-MS m/z: 489 [MH⁺]

Example 132

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}}-4-hydroxy-N-(4-hydroxycyclohexyl)benzamide

20 APCI-MS m/z: 530 [MH⁺]

Example 133

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}}-N-(2,3-dihydroxypropyl)-4-hydroxybenzamide

25 APCI-MS m/z: 507 [MH⁺]

Example 134

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}}-4-hydroxy-N-(2-hydroxyethyl)-N-methylbenzamide

30 APCI-MS m/z: 491 [MH⁺]

Example 135

methy1 N-(2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)serinate

5 APCI-MS m/z: 535 [MH⁺]

Example 136

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-N-(1-ethylpropyl)-4-hydroxybenzamide

10 APCI-MS m/z: 503 [MH⁺]

Example 137

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-(tetrahydrofuran-2-ylmethyl)benzamide

15 APCI-MS m/z: 517 [MH⁺]

Example 138

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-[1-(hydroxymethyl)-2,2-dimethylpropyl]benzamide

20 APCI-MS m/z: 533 [MH⁺]

Example 139

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-N-{{{(1S,2R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-yl}methyl}-4-hydroxybenzamide

25 APCI-MS m/z: 569 [MH⁺]

Example 140

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-[1-(hydroxymethyl)-2-methylpropyl]benzamide

30

APCI-MS m/z: 519 [MH⁺]

Example 141

3-{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-

5 hydroxypropyl]oxy}-4-{[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}phenol

APCI-MS m/z: 546 [MH⁺]

Example 142

3-{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-

10 hydroxypropyl]oxy}-4-{[3-(hydroxymethyl)piperidin-1-yl]carbonyl}phenol

APCI-MS m/z: 531 [MH⁺]

Example 143

2-{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-

15 hydroxypropyl]oxy}-N-[5-(1,1-dimethylpropyl)-2-hydroxyphenyl]-4-

hydroxybenzamide

APCI-MS m/z: 595 [MH⁺]

Example 144

20 2-{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-

hydroxypropyl]oxy}-4-hydroxy-N-[3-(1-hydroxyethyl)phenyl]benzamide

APCI-MS m/z: 553 [MH⁺]

Example 145

25 2-{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-

hydroxypropyl]oxy}-N-(cyclopropylmethyl)-4-hydroxybenzamide

APCI-MS m/z: 487 [MH⁺]

Example 146

2-[[[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-hydroxy-N-pyrrolidin-1-yl]benzamide
APCI-MS m/z: 502 [MH⁺]

5 **Example 147**

N-[(1R,4S)-bicyclo[2.2.1]hept-2-yl]-2-[[[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-hydroxybenzamide
APCI-MS m/z: 527 [MH⁺]

10 **Example 148**

4-(4-chlorophenyl)-1-(2-[[[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-hydroxybenzoyl]piperidin-4-ol
APCI-MS m/z: 627 [MH⁺]

15 **Example 149**

2-[[[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-hydroxy-N-(2-hydroxy-1-phenylethyl)benzamide
APCI-MS m/z: 553 [MH⁺]

20 **Example 150**

1-(2-[[[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-hydroxybenzoyl]-4-phenylpiperidin-4-ol
APCI-MS m/z: 593 [MH⁺]

25 **Example 151**

3-[[[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-(3,4-dihydroisoquinolin-2(1H)-ylcarbonyl)phenol
APCI-MS m/z: 549 [MH⁺]

30 **Example 152**

3-[[[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[[2-(hydroxymethyl)piperidin-1-yl]carbonyl]phenol
APCI-MS m/z: 531 [MH⁺]

5 **Example 153**

1-(2-[[[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-hydroxybenzoyl]-N,N-dimethylprolinamide
APCI-MS m/z: 558 [MH⁺]

10 **Example 154**

methyl (4R)-1-(2-[[[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-hydroxybenzoyl]-4-hydroxyprolinate
APCI-MS m/z: 561 [MH⁺]

15 **Example 155**

(3R)-1-(2-[[[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-hydroxybenzoyl]piperidin-3-ol
APCI-MS m/z: 517 [MH⁺]

20 **Example 156**

2-[[[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-hydroxy-N-(2-hydroxycyclohexyl)benzamide
APCI-MS m/z: 531 [MH⁺]

25 **Example 157**

3-[[[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-phenylpiperidin-1-yl)carbonyl]phenol
APCI-MS m/z: 577 [MH⁺]

30 **Example 158**

3-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-(thiomorpholin-4-ylcarbonyl)phenol
APCI-MS m/z: 519 [MH⁺]

5 **Example 159**

1-(2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)piperidin-3-ol
APCI-MS m/z: 517 [MH⁺]

10 **Example 160**

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-N-(cyclopropylmethyl)-4-hydroxy-N-propylbenzamide
APCI-MS m/z: 529 [MH⁺]

15 **Example 161**

2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N,N-diisobutylbenzamide
APCI-MS m/z: 545 [MH⁺]

20 **Example 162**

3-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-(1,3-dihydro-2H-isoindol-2-ylcarbonyl)phenol
APCI-MS m/z: 535 [MH⁺]

25 **Example 163**

N-(2-tert-butoxyethyl)-2-{{{(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-N-isobutylbenzamide
APCI-MS m/z: 589 [MH⁺]

30 **Example 164**

3-{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-fluoropiperidin-1-yl)carbonyl]phenol
APCI-MS m/z: 519 [MH⁺]

5 **Example 165**

3-{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4,4-difluoropiperidin-1-yl)carbonyl]phenol
APCI-MS m/z: 537 [MH⁺]

10 **Example 166**

2-{[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-N-phenylbenzamide
APCI-MS m/z: 493 [MH⁺]

- 15 The following compounds in Examples 167 to 211 were prepared as described in Example 124 using 6-Chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine] as starting material

Example 167

20 3-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-((2*R*)-2-[hydroxy(diphenyl)methyl]pyrrolidin-1-yl)carbonyl]phenol
APCI-MS m/z: 669 [MH⁺]

Example 168

25 2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-(2-hydroxyethyl)-*N*-methylbenzamide
APCI-MS m/z: 491 [MH⁺]

Example 169

3- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4-(pyrrolidin-1-ylcarbonyl)phenol
APCI-MS *m/z*: 487 [MH⁺]

5 **Example 170**

3- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4- $\{[4$ -(2-hydroxyethyl)piperazin-1-yl]carbonyl $\}$ phenol
APCI-MS *m/z*: 546 [MH⁺]

10 **Example 171**

3- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4- $\{[3$ -(hydroxymethyl)piperidin-1-yl]carbonyl $\}$ phenol
APCI-MS *m/z*: 531 [MH⁺]

15 **Example 172**

4-(4-chlorophenyl)-1-(2- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4-hydroxybenzoyl)piperidin-4-ol
APCI-MS *m/z*: 627 [MH⁺]

20 **Example 173**

3- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4- $\{[4$ -(hydroxymethyl)piperidin-1-yl]carbonyl $\}$ phenol
APCI-MS *m/z*: 531 [MH⁺]

25 **Example 174**

1-(2- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4-hydroxybenzoyl)-4-phenylpiperidin-4-ol
APCI-MS *m/z*: 593 [MH⁺]

30 **Example 175**

3- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4-(3,4-dihydroisoquinolin-2(1*H*)-ylcarbonyl)phenol
APCI-MS *m/z*: 549 [MH⁺]

5 **Example 176**

3- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4- $\{[2$ -(hydroxymethyl)piperidin-1-yl]carbonyl $\}$ phenol
APCI-MS *m/z*: 531 [MH⁺]

10 **Example 177**

3- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4- $\{[3$ -(dimethylamino)pyrrolidin-1-yl]carbonyl $\}$ phenol
APCI-MS *m/z*: 530 [MH⁺]

15 **Example 178**

1-(2- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4-hydroxybenzoyl)-*N,N*-dimethylprolinamide
APCI-MS *m/z*: 558 [MH⁺]

20 **Example 179**

2- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -*N*-cyclohexyl-4-hydroxy-*N*-(2-hydroxyethyl)benzamide
APCI-MS *m/z*: 559 [MH⁺]

25 **Example 180**

methyl (4*R*)-1-(2- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4-hydroxybenzoyl)-4-hydroxyprolinate
APCI-MS *m/z*: 561 [MH⁺]

30 **Example 181**

(3*R*)-1-(2-{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)piperidin-3-ol
APCI-MS *m/z*: 517 [MH⁺]

5 **Example 182**

3-{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-[(4-phenylpiperidin-1-yl)carbonyl]phenol
APCI-MS *m/z*: 577 [MH⁺]

10 **Example 183**

3-{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-(thiomorpholin-4-ylcarbonyl)phenol
APCI-MS *m/z*: 519 [MH⁺]

15 **Example 184**

1-(2-{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)piperidin-3-ol
APCI-MS *m/z*: 517 [MH⁺]

20 **Example 185**

2-{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-*N*-(cyclopropylmethyl)-4-hydroxy-*N*-propylbenzamide
APCI-MS *m/z*: 529 [MH⁺]

25 **Example 186**

2-{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-*N,N*-diisobutylbenzamide
APCI-MS *m/z*: 545 [MH⁺]

30 **Example 187**

3- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4-(1,3-dihydro-2*H*-isoindol-2-ylcarbonyl)phenol
APCI-MS *m/z*: 535 [MH⁺]

5 **Example 188**

N-(2-*tert*-butoxyethyl)-2- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4-hydroxy-*N*-isobutylbenzamide
APCI-MS *m/z*: 589 [MH⁺]

10 **Example 189**

3- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4-[(4-fluoropiperidin-1-yl)carbonyl]phenol
APCI-MS *m/z*: 519 [MH⁺]

15 **Example 190**

3- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4-[(4,4-difluoropiperidin-1-yl)carbonyl]phenol
APCI-MS *m/z*: 537 [MH⁺]

20 **Example 191**

2- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4-hydroxy-*N*-(2-hydroxypropyl)benzamide
APCI-MS *m/z*: 491 [MH⁺]

25 **Example 192**

2- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4-hydroxy-*N*-(2-hydroxy-1,1-dimethylethyl)benzamide
APCI-MS *m/z*: 505 [MH⁺]

30 **Example 193**

2- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -*N*-cyclopentyl-4-hydroxybenzamide
APCI-MS *m/z*: 501 [MH⁺]

5 **Example 194**

2- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4-hydroxy-*N*-(2-methoxyethyl)benzamide
APCI-MS *m/z*: 491 [MH⁺]

10 **Example 195**

2- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4-hydroxy-*N*-(2-hydroxyphenyl)benzamide
APCI-MS *m/z*: 525 [MH⁺]

15 **Example 196**

2- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4-hydroxy-*N*-(2-hydroxy-1-methylethyl)benzamide
APCI-MS *m/z*: 491 [MH⁺]

20 **Example 197**

2- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4-hydroxy-*N*-isobutylbenzamide
APCI-MS *m/z*: 489 [MH⁺]

25 **Example 198**

2- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4-hydroxy-*N*-(2-hydroxyethyl)benzamide
APCI-MS *m/z*: 477 [MH⁺]

30 **Example 199**

2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-*N*-(4-hydroxycyclohexyl)benzamide
APCI-MS *m/z*: 531 [*MH*⁺]

5 **Example 200**

2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-*N*-(2,3-dihydroxypropyl)-4-hydroxybenzamide
APCI-MS *m/z*: 507 [*MH*⁺]

10 **Example 201**

methyl *N*-(2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)serinate
APCI-MS *m/z*: 535 [*MH*⁺]

15 **Example 202**

2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-*N*-(1-ethylpropyl)-4-hydroxybenzamide
APCI-MS *m/z*: 503 [*MH*⁺]

20 **Example 203**

2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-*N*-(tetrahydrofuran-2-ylmethyl)benzamide
APCI-MS *m/z*: 517 [*MH*⁺]

25 **Example 204**

2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-*N*-[1-(hydroxymethyl)-2,2-dimethylpropyl]benzamide
APCI-MS *m/z*: 533 [*MH*⁺]

30 **Example 205**

2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-[1-(hydroxymethyl)-2-methylpropyl]benzamide
APCI-MS *m/z*: 519 [MH⁺]

5 **Example 206**

2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-[3-(1-hydroxyethyl)phenyl]benzamide
APCI-MS *m/z*: 553 [MH⁺]

10 **Example 207**

2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-(cyclopropylmethyl)-4-hydroxybenzamide
APCI-MS *m/z*: 487 [MH⁺]

15 **Example 208**

2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-pyrrolidin-1-ylbenzamide
APCI-MS *m/z*: 502 [MH⁺]

20 **Example 209**

N-[(1*R*,4*S*)-bicyclo[2.2.1]hept-2-yl]-2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzamide
APCI-MS *m/z*: 527 [MH⁺]

25 **Example 210**

2-{{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-(2-hydroxy-1-phenylethyl)benzamide
APCI-MS *m/z*: 553 [MH⁺]

30 **Example 211**

2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxy-*N*-(2-hydroxycyclohexyl)benzamide
APCI-MS *m/z*: 531 [*MH*⁺]

5 **Example 212**

1-(2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)pyrrolidine-3-carboxamide trifluoroacetate

Step I:

10 **1-{2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-[(4-methoxybenzyl)oxy]benzoyl}pyrrolidine-3-carboxamide**
A mixture of PS-carbodiimide (425 mg, 0.54 mmol) and dichloromethane (5 mL) was stirred at room temperature for 15 minutes, a solution of 2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-[(4-methoxybenzyl)oxy]benzoic acid hydrochloride (160 mg, 0.27 mmol) in NMP (2.5 mL)
15 and dichloromethane (2.5 mL) was added. The mixture was stirred for 30 minutes, and a mixture of pyrrolidine-3-carboxamide hydrochloride (73 mg, 0.48 mmol) and triethylamine (73 μ L, 52 mmol) in dichloromethane (2.5 mL) was added. The mixture was stirred at room temperature overnight and filtrated. Volatiles were removed in vacuo, the
20 residue was purified by HPLC (acetonitrile/water, 0.025% ammonium hydroxid) and gave (55 mg, yield 31%) of the subtitle compound.
APCI-MS: *m/z* 650 (*MH*⁺)

Step II:

25 **1-(2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxybenzoyl)pyrrolidine-3-carboxamide trifluoroacetate**
To a solution of 1-{2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-[(4-methoxybenzyl)oxy]benzoyl}pyrrolidine-3-carboxamide (55 mg, 0.084 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (0.3 mL).
30 The mixture was stirred at room temperature for 1 h, volatiles were removed, the residue

was purified by HPLC (acetonitrile/water, 0.1 % trifluoroacetic acid) to give 23 mg (42 %) of the title compound.

¹H-NMR (acetone-d₆, 400 MHz): δ 7.28-7.22 (m, 1H); 7.18-7.07 (m, 2H); 6.83-6.75 (m, 1H); 6.67-6.57 (m, 1H); 6.56-6.48 (m, 1H); 4.62-4.46 (m, 1H); 4.21-3.92 (m, 2H); 3.91-
5 3.44 (m, 8H); 3.44-3.26 (m, 2H); 3.26-3.06 (m, 3H); 2.50-2.01 (m, 6H).

APCI-MS: m/z 530 (MH⁺)

Example 213

1-(2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-
10 hydroxypropyl}oxy}-4-hydroxybenzoyl)-L-prolinamide trifluoroacetate

Step I:

1-{2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-
hydroxypropyl}oxy}-4-[(4-methoxybenzyl)oxy]benzoyl)-L-prolinamide

15 A mixture of PS-carbodiimide (425 mg, 0.54 mmol) and dichloromethane (3 mL) was stirred at room temperature for 15 minutes, a solution of 2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-[(4-methoxybenzyl)oxy]benzoic acid hydrochloride (160 mg, 0.27 mmol) in NMP (1.5 mL)
20 and dichloromethane (2 mL) was added. The mixture was stirred for 30 minutes, and a mixture of L-prolinamide (46 mg, 0.40 mmol) in dichloromethane (2 mL) was added. The mixture was stirred at room temperature overnight and filtrated. Volatiles were removed in vacuo, the residue was purified by HPLC (acetonitrile/water, 0.025% ammonium hydroxid) and gave 85 mg (48 %) of the subtitle compound.

25 APCI-MS: m/z 650 (MH⁺)

Step II:

1-(2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-
hydroxypropyl}oxy}-4-hydroxybenzoyl)-L-prolinamide trifluoroacetate

To a solution of 1-{2-[[*(2S)*-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoyl}-L-prolinamide (85 mg, 0.13 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (0.3 mL). The mixture was stirred at room temperature for 1 h, volatiles were removed, the residue was purified by HPLC (acetonitrile/water, 0.1 % trifluoroacetic acid) and gave 37 mg (44 %) of the title compound.

¹H-NMR (acetone-d₆, 400 MHz): δ 7.23 (s, 1H); 7.19-7.10, 7.06-7.03 and 6.61-6.54 (m, 5H); 6.77 (d, *J* = 8.3 Hz, 1H); 6.53-6.48 and 6.46-6.42 (m, 1H); 4.61-4.55 (m, 1H); 4.55-4.47 (m, 1H); 4.17-4.08 (m, 1H); 4.05-3.94 (m, 1H); 3.88-3.70 (m, 2H); 3.70-3.28 (m, 6H); 3.16 (br. s, 2H); 2.47-2.14 (m, 4H); 2.10-1.77 (m, 4H). The compound exists in solution as a mixture of 2 rotamers.

APCI-MS: *m/z* 530 (MH⁺)

Example 214

2-chloro-5-[[*(2S)*-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[[*(3R)*-3-(dimethylamino)pyrrolidin-1-yl]carbonyl]phenol bis(trifluoroacetate)

Step I:

methyl 5-chloro-2-hydroxy-4-[(4-methoxybenzyl)oxy]benzoate

A mixture of 1-(chloromethyl)-4-methoxybenzene (1.53 g, 9.8 mmol), methyl 5-chloro-2,4-dihydroxybenzoate (1.98 g, 9.8 mmol) and potassium carbonate (1.35 g, 9.8 mmol) in acetone (15 mL) was stirred at reflux overnight. The mixture was filtered, solvent was removed in vacuo, the residue was dissolved in ethyl acetate and was washed with brine two times. The organic layer was dried over sodium sulphate, solvent was removed in vacuo and the residue was purified by recrystallization from methanol. (1.46 g, 46 %) of the title compound was obtained.

¹H-NMR (CDCl₃, 400 MHz): δ 10.90 (s, 1H); 7.84 (s, 1H); 7.39 (d, *J* = 8.5 Hz, 2 H); 6.94 (d, *J* = 8.7 Hz, 2H); 6.57 (s, 1H); 5.10 (s, 2H); 3.93 (s, 3H); 3.83 (s, 3H).

Step II:**methyl 5-chloro-4-[(4-methoxybenzyl)oxy]-2-[(2*S*)-oxiran-2-ylmethoxy]benzoate**

A mixture of methyl 5-chloro-2-hydroxy-4-[(4-methoxybenzyl)oxy]benzoate (1.78 g, 5.5 mmol), (2*S*)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (1.43 g, 5.5 mmol) and cesiumcarbonate (2.15 g, 6.6 mmol) in NMP (15 mL) was stirred at room temperature overnight. Water was added to the mixture and it was then extracted with ethyl acetate three times. The combined organic layers was washed with water, dried over sodium sulphate and solvent was removed in vacuo. The residue was purified by silica gel flash chromatography (ethyl acetate / heptane 10-30 %), (1.66 g, 79 %) of the title compound was obtained.

¹H-NMR (CDCl₃, 300 MHz): δ 7.92 (s, 1H); 7.39 (d, *J* = 8.8 Hz, 2H); 6.93 (d, *J* = 8.7 Hz, 2H); 6.67 (s, 1H); 5.15 (s, 2H); 4.35 (dd, *J* = 2.5, 11.5 Hz, 1H); 4.02-3.96 (m, 1H); 3.87 (s, 1H); 3.83 (s, 3H); 3.41-3.35 (m, 1H); 2.95-2.88 (m, 2H).

APCI-MS: *m/z* 379 (MH⁺)

Step III:**methyl 5-chloro-2-[[[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoate**

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (420 mg, 1.9 mmol) and methyl 5-chloro-4-[(4-methoxybenzyl)oxy]-2-[(2*S*)-oxiran-2-ylmethoxy]benzoate (710 mg, 1.9 mmol) in ethanol (15 mL) was stirred and heated at reflux overnight. Solvent was removed in vacuo, the residue required no further purification, (1.13 g, 100%) of the title compound was obtained.

APCI-MS: *m/z* 602 (MH⁺)

Step IV:**5-chloro-2-[[[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoic acid hydrochloride**

A mixture of methyl 5-chloro-2- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4- $\{[(4$ -methoxybenzyl)oxy]benzoate (1.13 g, 1.9 mmol), potassium hydroxide (15 g), water (15 mL) and ethanol (50 mL) was stirred at room temperature for two hours. Ethanol was removed in vacuo, aqueous hydrochloric acid (37 %) was added until pH = 1, the mixture was extracted with ethyl acetate, washed with brine and dried with sodium sulphate. Solvent was removed in vacuo, no further purification was needed, (1.05 g, 89 %) of the title compound was obtained.
APCI-MS: m/z 588 (MH⁺)

Step V:

(2*S*)-1-{4-chloro-2- $\{[(3R)$ -3-(dimethylamino)pyrrolidin-1-yl]carbonyl $\}$ -5- $\{[(4$ -methoxybenzyl)oxy]phenoxy $\}$ -3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propan-2-ol

A mixture of PS-carbodiimide (380 mg, 0.49 mmol) and dichloromethane (3 mL) was stirred at room temperature for 15 minutes, a solution of 5-chloro-2- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4- $\{[(4$ -methoxybenzyl)oxy]benzoic acid hydrochloride (150 mg, 0.24 mmol) in NMP (0.5 mL) and dichloromethane (2.5 mL) was added. The mixture was stirred for 30 minutes, and a mixture of (3*R*)-*N,N*-dimethylpyrrolidin-3-amine (56 mg, 0.49 mmol) in dichloromethane (2.5 mL) was added. The mixture was stirred at room temperature overnight and filtrated. Volatiles were removed in vacuo, the residue was purified by HPLC (acetonitrile/water, 0.025% ammonium hydroxid) and gave 110 mg, (67%) of the subtitle compound.
APCI-MS: m/z 684 (MH⁺)

Step VI:

2-chloro-5- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4- $\{[(3R)$ -3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenol bis(trifluoroacetate)

To a solution of (2*S*)-1-{4-chloro-2-[[*(3R)*-3-(dimethylamino)pyrrolidin-1-yl]carbonyl}-5-
[[*(4*-methoxybenzyl)oxy]phenoxy}-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-
1'-yl)propan-2-ol (110 mg, 0.16 mmol) in dichloromethane (3 mL) was added

trifluoroacetic acid (0.3 mL). The mixture was stirred at room temperature for 1 hour,

5 volatiles were removed, the residue was purified by HPLC (acetonitrile/water, 0.1 %

trifluoroacetic acid) and gave 45 mg (35 %) of the title compound.

¹H-NMR (acetone-*d*₆, 400 MHz): δ 7.24-7.21 (m, 2H); 7.13 (d, *J* = 8.9 Hz, 1H); 7.07 and
6.98 (m, 1H); 6.77 (d, *J* = 8.5 Hz, 1H); 4.66-4.50 (m, 1H); 4.20-3.96 (m, 2H); 3.94-3.70
(m, 2H); 3.68-3.46 (m, 4H); 3.44-3.35 (m, 1H); 3.19 (br. s, 2H); 2.97 (s, 3H); 2.93 (s, 3H);

10 2.58-2.19 (m, 6H). The compound exists in solution as a mixture of 2 rotamers.

APCI-MS: *m/z* 564 (MH⁺)

Example 215

2-chloro-5-[[*(2S)*-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-
15 hydroxypropyl]oxy]-4-[[*(3R)*-3-(hydroxymethyl)pyrrolidin-1-yl]carbonyl]phenol
trifluoroacetate

Step I:

(2*S*)-1-{4-chloro-2-[[*(3R)*-3-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}-5-[[*(4*-
20 methoxybenzyl)oxy]phenoxy}-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-
1'-yl)propan-2-ol

A mixture of PS-carbodiimide (380 mg, 0.49 mmol) and dichloromethane (3 mL) was
stirred at room temperature for 15 minutes, a solution of 5-chloro-2-[[*(2S)*-3-(5-chloro-

1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[[*(4*-

25 methoxybenzyl)oxy]benzoic acid hydrochloride (150 mg, 0.24 mmol) in NMP (1 mL) and
dichloromethane (2.5 mL) was added. The mixture was stirred for 30 minutes, and a

mixture of (*3R*)-pyrrolidin-3-ylmethanol (82 mg, 0.59 mmol) and triethylamine (85 μL, 61
mmol) in dichloromethane (2.5 mL) was added. The mixture was stirred at room

temperature for 48 h and was then filtered. Volatiles were removed in vacuo, the residue

was purified by HPLC (acetonitrile/water, 0.025% ammonium hydroxid) and gave 87 mg (54 %) of the subtitle compound.

APCI-MS: m/z 671 (MH^+)

5 **Step II:**

2-chloro-5-(((2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl)oxy)-4-(((3*R*)-3-(hydroxymethyl)pyrrolidin-1-yl)carbonyl}phenol trifluoroacetate

To a solution of (2*S*)-1-{4-chloro-2-(((3*R*)-3-(hydroxymethyl)pyrrolidin-1-yl)carbonyl)-5-
10 [(4-methoxybenzyl)oxy]phenoxy}-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propan-2-ol (87 mg, 0.13 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (0.3 mL). The mixture was stirred at room temperature for 1 hour, volatiles were removed, the residue was purified by HPLC (acetonitrile/water, 0.1 % trifluoroacetic acid) and gave 23 mg (26 %) of the title compound.

15 ¹H-NMR (acetone- d_6 , 300 MHz): δ 7.24-7.21 (m, 2H); 7.13 (dd, $J = 2.4, 8.6$ Hz, 1H); 6.97-6.92 (m, 1H); 6.77 (dd, $J = 1.2, 8.6$ Hz, 1H); 4.57-4.46 (m, 1H); 4.18-4.04 (m, 2H); 3.92-3.70 (m, 2H); 3.70-3.30 (m, 10H); 3.29-3.12 (m, 3H); 2.52-2.16 (m, 4H); 2.10-1.68 (m, 2H).

APCI-MS: m/z 551 (MH^+)

20

Example 216

2-chloro-5-(((2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl)oxy)-4-(((3*S*)-3-(hydroxymethyl)pyrrolidin-1-yl)carbonyl}phenol trifluoroacetate

25 The title compound was prepared using (3*S*)-pyrrolidin-3-ylmethanol as described in Example 215.

¹H-NMR (acetone- d_6 , 300 MHz): δ 7.26-7.21 (m, 2H); 7.13 (dd, $J = 2.3, 8.5$ Hz, 1H); 6.97-6.90 (m, 1H); 6.77 (dd, $J = 1.2, 8.4$ Hz, 1H); 4.56-4.46 (m, 1H); 4.17-4.03 (m, 2H); 3.92-3.70 (m, 2H); 3.70-3.33 (m, 10H); 3.30-3.22 (m, 1H); 3.17 (br. s, 2H); 2.52-2.16 (m, 4H);
30 2.10-1.68 (m, 2H).

APCI-MS: m/z 551 (MH⁺)

Example 217

2-chloro-5-{[(2*S*)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-(pyrrolidin-1-ylcarbonyl)phenol trifluoroacetate

Step I:

methyl 5-chloro-2-{[(2*S*)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoate

10 A mixture of 5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (390 mg, 1.9 mmol) and methyl 5-chloro-4-[(4-methoxybenzyl)oxy]-2-[(2*S*)-oxiran-2-ylmethoxy]benzoate (710 mg, 1.9 mmol) in ethanol (15 mL) was stirred and heated at reflux overnight. Solvent was removed in vacuo, the residue was purified by silica gel flash chromatography (dichloromethane / methanol 0-3 %), and gave the subtitle compound.

15 APCI-MS: m/z 586 (MH⁺)

Step II:

5-chloro-2-{[(2*S*)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoic acid hydrochloride

20 A mixture of methyl 5-chloro-2-{[(2*S*)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoate (910 mg, 1.5 mmol), potassium hydroxide (15 g), water (15 mL) and ethanol (50 mL) was stirred at room temperature for three hours. Ethanol was removed in vacuo, aqueous hydrochloric acid (37 %) was added until pH = 1, the mixture was extracted with ethyl acetate, washed
25 with brine and dried with sodium sulphate. Solvent was removed in vacuo, no further purification was needed. 0.91 g (80 % overall yield for Steps I-II) of the title compound were obtained.

APCI-MS: m/z 572 (MH⁺)

30 **Step III:**

(2*S*)-1-[4-chloro-5-[(4-methoxybenzyl)oxy]-2-(pyrrolidin-1-ylcarbonyl)phenoxy]-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propan-2-ol

A mixture of PS-carbodiimide (380 mg, 0.49 mmol) and dichloromethane (3 mL) was stirred at room temperature for 15 minutes, a solution of 5-chloro-2-
5 1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoic acid hydrochloride (150 mg, 0.25 mmol) in NMP (0.5 mL) and dichloromethane (2.5 mL) was added. The mixture was stirred for 30 minutes, and a mixture of pyrrolidine (56 mg, 0.49 mmol) in dichloromethane (2.5 mL) was added. The mixture was stirred at room temperature for 48 hours and was then filtrated. Volatiles were
10 removed in vacuo, the residue was purified by HPLC (acetonitrile/water, 0.025% ammonium hydroxid) and gave (45 mg, yield 29 %) of the subtitle compound.

APCI-MS: *m/z* 625 (*MH*⁺)

Step IV:

**2-chloro-5-
15 2-[[[(2*S*)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-(pyrrolidin-1-ylcarbonyl)phenol trifluoroacetate**

To a solution of (2*S*)-1-[4-chloro-5-[(4-methoxybenzyl)oxy]-2-(pyrrolidin-1-ylcarbonyl)phenoxy]-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propan-2-ol (45 mg, 0.07 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (0.3
20 mL). The mixture was stirred at room temperature for 1 hour, volatiles were removed, the residue was purified by HPLC (acetonitrile/water, 0.1 % trifluoroacetic acid) and gave 38 mg (87 %) of the title compound.

¹H-NMR (acetone-*d*₆, 300 MHz): δ 7.24 (s, 1H); 7.04-6.98 (m, 1H); 6.97-6.94 (m, 1H); 6.94-6.84 (m, 1H); 6.77-6.72 (m, 1H); 4.56-4.45 (m, 1H); 4.17-4.06 (m, 2H); 3.90-3.69 (m,
25 2H); 3.60-3.44 (m, 4H); 3.44-3.28 (m, 4H); 3.16 (br. s, 2H); 2.46-2.14 (m, 4H); 2.00-1.82 (m, 4H).

APCI-MS: *m/z* 505 (*MH*⁺)

Example 218

***N*-(2-(((2R)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl)oxy)-4-methoxyphenyl)acetamide**

5 Step I

(2R)-2-[(5-Methoxy-2-nitrophenoxy)methyl]oxirane

To a mixture of (2S)-oxiran-2-ylmethanol (296.3 mg, 4.0 mmol), 5-methoxy-2-nitrophenol (676.6 mg, 4.0 mmol) and triphenyl phosphine (1.05 g, 4.0 mmol) in THF (10 mL) was added diethyl azodicarboxylate (DEAD, 704.6 mg, 4.0 mmol) in THF (5 mL) dropwise at
10 room temperature. After addition was completed the reaction mixture was stirred at room temperature overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-40% ethyl acetate in petroleum spirit) to give the subtitled compound (650 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 8.00 (d, *J* = 9.0 Hz, 1H), 6.60 (d, *J* = 2.5 Hz, 1H); 6.55 (dd, *J* = 2.5, 9.2 Hz, 1H); 4.41 (dd, *J* = 2.7, 11.3 Hz, 1H); 4.12 (dd, *J* = 5.0, 11.3 Hz, 1H); 3.90 (s, 3H); 3.41 (m, 1H); 2.93 (m, 2H).
15

Step II

***N*-(4-Methoxy-2-[(2R)-oxiran-2-ylmethoxy]phenyl)acetamide**

20 A mixture of (2R)-2-[(5-methoxy-2-nitrophenoxy)methyl]oxirane (620 mg, 2.75 mmol), Pd on charcoal (10%) (250 mg), *N*-ethyl-diisopropylamine (0.941 mL), acetic anhydride (0.52 mL, 5.5 mmol) in ethyl acetate (25 mL) was hydrogenated at normal pressure for 40 min. The catalyst was filtered off and the filtrate was concentrated. The residue was purified by silica gel flash chromatography (0-60% ethyl acetate in petroleum spirit) to
25 give the subtitled compound (155 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 8.21 (d, *J* = 8.7 Hz, 1H); 6.52 (m, 2H); 4.35 (dd, *J* = 2.5, 11.4 Hz, 1H); 3.93 (dd, *J* = 6.0, 11.4 Hz, 1H); 3.80 (s, 3H); 3.40 (m, 1H); 2.96 (t, *J* = 4.6 Hz, 1H); 2.78 (dd, *J* = 2.7, 4.8 Hz, 1H).

APCI-MS: *m/z* 238(MH⁺).

Step III***N*-(2-{{{(2R)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-methoxyphenyl)acetamide**

A mixture of 5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine]hydrochloride (154 mg, 0.632 mmol), *N*-{4-Methoxy-2-[(2R)-oxiran-2-ylmethoxy]phenyl}acetamide (150 mg, 0.632 mmol) and K₂CO₃ (87 mg, 0.632 mmol) in ethanol (3 mL) was stirred at 80 °C for 3h. The reaction mixture was partitioned between ethyl acetate and H₂O. The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (100 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 8.18 (d, *J* = 8.6 Hz, 1H); 8.02 (br.s, 1H); 6.87 (m, 1H); 6.80 (m, 1H); 6.66 (dd, *J* = 4.2, 8.7 Hz, 1H); 6.56-6.51 (m, 2H); 4.18 (m, 1H); 4.04 (dd, *J* = 3.3, 10.1 Hz, 1H); 3.96 (dd, *J* = 5.7, 10.1 Hz, 1H); 3.79 (s, 3H); 3.01 (s, 2H); 2.91 (m, 2H); 2.78-2.57 (m, 4H); 2.20 (s, 3H); 2.07-1.84 (m, 4H).

APCI-MS: *m/z* 445(MH⁺).

Example 219**Methyl 2-{{{(2S)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}benzoate**

A mixture of 5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (155.4 mg, 0.75 mmol) and methyl 2-[(2S)-oxiran-2-ylmethoxy]benzoate (157 mg, 0.75 mmol) in methanol (4 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.1% NH₄OH) to give the titled compound (250 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 7.83 (dd, *J* = 1.9, 4.1 Hz, 1H); 7.48 (m, 1H); 7.02 (m, 2H); 6.86 (m, 1H); 6.79 (m, 1H); 6.66 (dd, *J* = 4.2, 8.7 Hz, 1H); 4.26-4.16 (m, 2H); 4.09 (dd, *J* = 5.7, 9.2 Hz, 1H); 3.90 (s, 3H); 3.00 (s, 2H); 2.90-2.68 (m, 6H); 2.00 (m, 2H); 1.90 (m, 2H).

APCI-MS: *m/z* 416(MH⁺).

Example 220**2-{[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}benzoic acid (hydrochloride)**

Methyl 2-{[(2S)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-

hydroxypropyl]oxy}benzoate (240 mg, 0.58 mmol) was dissolved in THF (4 mL), aqueous KOH (67 mg KOH in 1 mL H₂O) was added and the reaction mixture was stirred at room temperature overnight. The pH of the reaction mixture was adjusted to 2.0 by addition of aqueous HCl, extracted with ethyl acetate. The organic layer was washed with H₂O, dried over Na₂SO₄, filtered and concentrated to give the titled compound (210 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.93 (dd, *J* = 1.8, 7.8 Hz, 1H); 7.57 (m, 1H); 7.18 (d, *J* = 8.4 Hz, 1H); 7.10 (t, *J* = 7.6 Hz, 1H); 6.97 (dd, *J* = 2.6, 8.1 Hz, 1H); 6.85 (m, 1H); 6.73 (dd, *J* = 4.2, 8.8 Hz, 1H); 4.46 (m, 1H); 4.31 (dd, *J* = 4.0, 9.5 Hz, 1H); 4.15 (dd, *J* = 5.4, 9.5 Hz, 1H); 3.76-3.40 (m, 6H); 3.16 (s, 2H); 2.30 (m, 2H); 2.19 (m, 2H).

APCI-MS: *m/z* 403(MH⁺).

Example 221**(3S)-1-(2-{[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}benzoyl)pyrrolidin-3-ol**

A mixture of 2-{[(2S)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-

hydroxypropyl]oxy}benzoic acid (hydrochloride) (200 mg, 0.456 mmol) and *N,N*-carbonyldiimidazole (89 mg, 0.548 mmol) in DMF (3 mL) was stirred at room temperature for 40 min, a solution of 3(S)-pyrrolidin-3-ol (199 mg, 2.28 mmol) in DMF (1 mL) was added and the reaction mixture was stirred at room temperature overnight. The mixture was partitioned between ethyl acetate and H₂O, organic layer was dried over Na₂SO₄,

filtered and concentrated. The residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (96 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.42 (m, 1H); 7.27 (d, *J* = 7.4 Hz, 1H); 7.11 (dd, *J* = 2.8, 8.4 Hz, 1H); 7.04 (t, *J* = 7.4 Hz, 1H); 6.90 (dd, *J* = 2.5, 8.0 Hz, 1H); 6.78 (m, 1H); 6.63 (dd, *J* = 4.2, 8.7 Hz, 1H); 4.50 (m, 0.5 H); 4.38 (m, 0.5H); 4.17-4.00 (m, 3H); 3.72 (m 1H);

3.63 (m, 1H); 3.50 (m, 1H); 3.373.18 (m, 1H, under methanol peak); 3.02 (s, 2H); 2.77-2.54 (m, 6H); 2.18-1.78 (m, 6H).

APCI-MS: m/z 471(MH^+).

5 **Example 222**

3-[[[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-(pyrrolidin-1-ylcarbonyl)phenol

Step I

10 **Methyl 2-[[[(2S)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoate**

A mixture of 5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (119 mg, 0.577 mmol) and methyl 4-[(4-methoxybenzyl)oxy]-2-[(2S)-oxiran-2-ylmethoxy] benzoate (199 mg, 0.577 mmol) in methanol (3 mL) was stirred at 80 °C overnight. The volatiles were removed in
15 vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH_4OH) to give the subtitled compound (228 mg).

1H -NMR ($CDCl_3$, 400 MHz): δ 7.85 (d, J = 8.6 Hz, 1H); 7.36 (d, J = 8.6 Hz, 1H); 6.94 (m, 2H); 6.89-6.77 (m, 2H); 6.66 (dd, J = 4.1, 8.7 Hz, 1H); 6.62-6.57 (m, 2H); 4.28 (m, 1H); 4.12 (dd, J = 4.7, 9.3 Hz, 1H); 4.06 (dd, J = 5.9, 9.3 Hz, 1H); 3.88 (s, 3H); 3.85 (s, 3H);
20 3.00 (s, 2H); 2.98-2.74 (m, 6H); 2.00 (br,s, 4H).

APCI-MS: m/z 552(MH^+).

Step II

2-[[[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoic acid (hydrochloride)
25

Methyl 2-[[[(2S)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoate (220 mg, 0.398 mmol) was taken in ethanol (3 mL), aqueous KOH (224 mg, KOH in 1 mL H_2O) was added and the mixture was stirred at reflux temperature overnight, cooled to 0 °C, aqueous HCl was added until

pH became 2.0, extracted with ethyl acetate, washed with H₂O, dried over Na₂SO₄, filtered and concentrated to give the subtitled compound (180 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.90 (d, *J* = 9.1 Hz, 1H); 7.36 (d, *J* = 8.7 Hz, 2H); 6.98-6.91 (m, 3H); 6.83 (m, 1H); 6.74-6.68 (m, 3H); 5.10 (s, 2H); 4.44 (m, 1H); 4.27 (dd, *J* = 4.0, 9.4 Hz, 1H); 4.10 (dd, *J* = 5.4, 9.4 Hz, 1H); 3.80 (s, 3H); 3.77-3.40 (m, 6H); 3.12 (s, 2H); 2.30 (m, 2H); 2.15 (m, 2H).

APCI-MS: *m/z* 538(MH⁺).

Step III

(2S)-1-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-[5-[(4-methoxybenzyl)oxy]-2-(pyrrolidin-1-ylcarbonyl)phenoxy]propan-2-ol 2-[[[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoic acid (hydrochloride) (136 mg, 0.237 mmol) and *N,N*-carbonyldiimidazole (46 mg, 0.284 mmol) was taken in DMF (3 mL) and stirred at room temperature for 55 min, pyrrolidine (168.5 mg, 2.37 mmol) was added and stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and H₂O. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH₄OH) to give the sub titled compound (70 mg). APCI-MS: *m/z* 552(MH⁺).

Step IV

3-[[[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-(pyrrolidin-1-ylcarbonyl)phenol

(2S)-1-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-[5-[(4-methoxybenzyl)oxy]-2-(pyrrolidin-1-ylcarbonyl)phenoxy]propan-2-ol (65 mg, 0.11 mmol) was treated with 10% CF₃CO₂H in CH₂Cl₂ (3 mL) for 25 min at room temperature. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2.5% methanol in dichloromethane, 0.2% NH₄OH) to give the titled compound (28 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.07 (d, *J* = 8.2 Hz, 1H); 6.90 (dd, *J* = 2.6, 8.2 Hz, 1H); 6.77 (m, 1H); 6.63 (dd, *J* = 4.2, 8.7 Hz, 1H); 6.50 (d, *J* = 2.1 Hz, 1H); 6.44 (dd, *J* = 2.1, 8.3 Hz, 1H); 4.10 (m, 1H); 4.03 (dd, *J* = 4.3, 9.7 Hz, 1H); 3.96 (dd, *J* = 5.6, 9.7 Hz, 1H); 3.56 (t, *J* = 7.0 Hz, 2H); 3.34 (m, 2H, inside methanol peak); 3.01 (s, 2H); 2.70 (br.s, 4H); 2.56 (m, 2H); 2.01-1.78 (m, 8H).
APCI-MS: *m/z* 471 (MH⁺).

Example 223

N-(4-fluoro-2-(((2*S*)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl)oxy}phenyl)acetamide

The title compound was prepared using 5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine] as described in Example 2.

¹H-NMR (acetone-*d*₆, 300 MHz): δ 8.63 (br. s, 1H); 8.26-8.17 (m, 1H); 6.99-6.88 (m, 2H); 6.87-6.76 (m, 1H); 6.74-6.62 (m, 2H); 4.25-4.19 (m, 1H); 4.19-4.09 (m, 1H); 4.07-3.99 (m, 1H); 3.03 (s, 2H); 2.85 (br. s, 1H); 2.78-2.60 (m, 4H); 2.60-2.54 (m, 2H); 2.10 (s, 3H); 1.97-1.76 (m, 4H).
APCI-MS: *m/z* 433 (MH⁺)

Example 224

N-{5-chloro-2-[3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl}cyclopentanecarboxamide

Step 1:

5-chloro-6-[(triisopropylsilyl)oxy]-1,3-benzoxazol-2(3*H*)-one

5-chloro-6-hydroxy-1,3-benzoxazol-2(3*H*)-one (0.93 g, 5 mmol) and imidazole (1.00 g, 15 mmol) were dissolved in dimethylformamide (10 mL) with stirring under inert atmosphere. Triisopropylsilylchloride (1.15 g, 6 mmol) was added and the resulting solution was stirred for 3 days. The reaction mixture was partitioned between water and heptane. The organic

layer was washed with water and dried over magnesium sulphate, filtrated and concentrated, to give 1.45 g (85%) of the subtitled compound as a grey solid.

APCI-MS: m/z 342 [MH⁺]

5 **Step II:**

N-{5-chloro-2-hydroxy-4-[(triisopropylsilyl)oxy]phenyl}cyclopentanecarboxamide
Bromo(cyclopentyl)magnesium (0.58 mL, 1.16 mmol, 2 M in diethylether) was added under inert atmosphere to a solution of 5-chloro-6-[(triisopropylsilyl)oxy]-1,3-benzoxazol-2(3*H*)-one (66 mg, 0.19 mmol) in tetrahydrofuran (3 mL). After stirring over night at 70°C,
10 the solution was evaporated and dissolved in ethylacetate. The organic layer was washed with water and 1M hydrochloric acid, dried and finally concentrated to give 68 mg (89%) of the subtitled compound as a brown solid.

APCI-MS: m/z 412 [MH⁺]

15 **Step III:**

N-{5-chloro-2-(oxiran-2-ylmethoxy)-4-[(triisopropylsilyl)oxy]phenyl}-cyclopentanecarboxamide

N-{5-chloro-2-hydroxy-4-[(triisopropylsilyl)oxy]phenyl}cyclopentanecarboxamide (140 mg, 0.3 mmol) was dissolved in 1,4-dioxane (20 mL). Caesium carbonate (170 mg, 0.5
20 mmol) was added, followed by (2*S*)-oxiran-2-yl-methyl 3-nitrobenzenesulfonate (90 mg, 0.3 mmol). After stirring over night at room temperature the mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and concentrated. Purification by HPLC on C18 (Xterra, 5 μ m, 19x50 mm; acetonitrile/water 60/40 to 100/0 over 15 min) yielded 25 mg (17%) of the titled intermediate compound.
25 ¹H-NMR (300 MHz, (CDCl₃) δ : 8.45 (1H, s); 7.70 (1H, bs); 6.51 (1H, s); 4.27 (1H, dd); 3.88 (1H, dd); 3.39-3.34 (1H, m); 2.98-2.95 (1H, m); 2.80 (1H, dd); 2.79-2.67 (1H, m); 2.02-1.61 (8H, m); 1.36-1.22 (3H, m); 1.17-1.05 (18H, m)

APCI-MS: m/z 468 [MH⁺]

30 **Step IV:**

N-{5-chloro-2-[3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl}cyclopentanecarboxamide

A solution of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (11 mg, 0.05 mmol) and N-{5-chloro-2-(oxiran-2-ylmethoxy)-4-[(triisopropylsilyl)oxy]phenyl}cyclopentane-
5 carboxamide (25 mg, 0.05 mmol) in isopropanol (15 mL) was stirred over night at 65°C, and then concentrated to give 34 mg (98%) of N-{5-chloro-2-[3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(triisopropylsilyl)oxy]phenyl}-cyclopentanecarboxamide as a light brown solid, which was dissolved in dimethylformamide (15 mL) and water (1.5 mL). Caesium carbonate (32 mg, 0.10 mmol)
10 was added. The solution was stirred over night at room temperature, and then partitioned between water and ethyl acetate. The organic layer was washed several times with water, dried and concentrated. The residue was purified by HPLC on C18 (Kromasil, 5 μ m, acetonitrile/water 10/90 to 60/40 over 20 min) to give the titled compound.

APCI-MS: *m/z* 535 [MH⁺]

Example 225

N-{5-chloro-2-[3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl}cyclopentanecarboxamide

20 The title compound was prepared as described in Example 224 using 5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine].

APCI-MS: *m/z* 519 [MH⁺]

Example 226

N-{5-chloro-4-hydroxy-2-[2-hydroxy-3-(1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]phenyl}cyclopentanecarboxamide

The title compound was prepared as described in Example 224 using 3*H*-spiro[1-benzofuran-2,4'-piperidine].

30 APCI-MS: *m/z* 501 [MH⁺]

Example 227

***N*-(5-Chloro-2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxyphenyl)benzamide trifluoroacetate (salt)**

5

Step I:***N*-(5-Chloro-2,4-dimethoxyphenyl)benzamide**

To a stirred solution of (5-chloro-2,4-dimethoxyphenyl)amine (1.88 g, 10 mmol) and triethylamine (2.1 mL, 15 mmol) in DCM (50 mL) benzoylchloride (1.3 mL, 11 mmol) was added dropwise while cooled. The reaction was complete in 5. The solution was washed consecutively with 1M sodium hydrogencarbonate solution (10 mL) and water (3 x 10 mL), dried and concentrated *in vacuo* leaving a solid, which was recrystallized from ethylacetate (25 mL) to give a pale gray solid (1.975 g, 67%).

APCI-MS: *m/z* 292 (MH⁺)

15

Step II:***N*-(5-Chloro-2,4-dihydroxyphenyl)benzamide**

To a stirred solution of *N*-(5-chloro-2,4-dimethoxyphenyl)benzamide (292 mg, 1 mmol) in DCM (10 mL) 1M boron tribromide in DCM (3 mL, 3 mmol) was added dropwise at ambient temperature. A precipitate was formed after 30 min. The stirring was continued over night. The mixture was quenched with methanol (5 mL) and concentrated *in vacuo* leaving an oil which was used without further purification.

APCI-MS: *m/z* 264 (MH⁺)

Step III:**4-(Benzoylamino)-2-chloro-5-hydroxyphenyl benzoate**

To crude *N*-(5-chloro-2,4-dihydroxyphenyl)benzamide (1 mmol) in acetone (10 mL) potassium carbonate (280 mg, 2 mmol) and benzoylchloride (140 mg, 1 mmol) was added. The mixture was stirred at ambient temperature over night. The solvent was removed *in*

25

vacuo and the residue purified by flash chromatography on silica using DCM and methanol in gradient. The pure compound was obtained as a white solid (153 mg, 42%).

¹H-NMR (Aceton-*d*₆, 400 MHz): δ 9.81 (bs, 1H); 9.39 (bs, 1H); 8.21 (d, *J* = 7.3 Hz, 2H); 8.16 (s, 1H); 8.06 (d, *J* = 7.3 Hz, 2H); 7.77 (t, *J* = 7.6 Hz, 1H); 7.68-7.55 (m, 5H); 7.07 (s, 1H)

APCI-MS: *m/z* 368 (MH⁺)

Step IV:

4-(Benzoylamino)-2-chloro-5-[(2*S*)-oxiran-2-ylmethoxy]phenyl benzoate

To a stirred solution of 4-(benzoylamino)-2-chloro-5-hydroxyphenyl benzoate (103 mg, 0.28 mmol) and [(2*S*)-2-methyloxiran-2-yl]methyl 3-nitrobenzenesulfonate (73 mg, 0.28 mmol) in DMF (3 mL) cesium carbonate (98 mg, 0.3 mmol) was added. The stirring was continued at ambient temperature over night. The mixture was poured into water and partitioned between water and ethylacetate. The organic phase was washed with water, dried and concentrated *in vacuo* to give a white solid (117 mg, 98%). The solid was used without further purification.

¹H-NMR (Aceton-*d*₆, 400 MHz): δ 9.06 (bs, 1H); 8.66 (s, 1H); 8.22 (d, *J* = 7.5 Hz, 2H); 8.02 (d, *J* = 7.5 Hz, 2H); 7.77 (t, *J* = 7.7 Hz, 1H); 7.64 (t, *J* = 7.7 Hz, 2H); 7.57 (t, *J* = 7.7 Hz, 2H); 7.30 (s, 1H); 4.57 (dd, *J* = 2.4, 11.5 Hz, 1H); 4.11 (dd, *J* = 6.2, 11.5 Hz, 1H); 3.49-3.43 (m, 1H); 2.90-2.87 (m, 1H); 2.81-2.78 (m, 2H)

APCI-MS: *m/z* 424 (MH⁺)

Step V:

N-(5-Chloro-2-{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)benzamide trifluoroacetate (salt)

A solution of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (29 mg, 0.13 mmol) and 4-(benzoylamino)-2-chloro-5-[(2*S*)-oxiran-2-ylmethoxy]phenyl benzoate (55 mg, 0.13 mmol) in ethanol (3 mL) was stirred at 80°C for 2h. 1M NaOH (0.15 mL, 0.15 mmol) was added and the stirring continued at 80°C for 1h. The solvent was evaporated *in vacuo* and the crude product purified by flash chromatography (silica, DCM and methanol in

gradient) leaving an oil (32 mg), which was dissolved in acetic acid and acidified with TFA. After freeze drying the titled compound was obtained as an amorphous solid (36 mg, 42%).
¹H-NMR (Aceton-*d*₆, 400 MHz): δ 9.01 (s, 1H); 8.95 (bs, 1H); 8.24 (s, 1H); 8.23 (s, 1H); 8.03-7.98 (m, 2H); 7.59-7.49 (m, 3H); 7.24-7.22 (m, 1H); 7.14 (dd, *J* = 8.5, 2.3 Hz, 1H);
5 6.92 (s, 1H); 6.76 (d, *J* = 8.5 Hz, 1H); 4.66-4.58 (m, 1H); 4.21-4.12 (m, 2H); 3.80-3.53 (m, 3H); 3.53-3.36 (m, 3H); 3.17 (s, 2H); 2.38-2.16 (m, 4H)
APCI-MS: *m/z* 543 (MH⁺)

Example 228

10 *N*-(5-Chloro-2-{{{(2*S*)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxyphenyl)benzamide trifluoroacetate (salt)

The compound was prepared using 5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine] as described in Example 227.

15 ¹H-NMR (Aceton-*d*₆, 400 MHz): δ 9.02 (bs, 2H); 8.23 (s, 1H); 8.22 (s, 1H); 8.01 (d, *J* = 7.3 Hz, 2H); 7.59-7.49 (m, 3H); 7.01 (d, *J* = 8.3 Hz, 1H); 6.94 (s, 1H); 6.88 (ddd, *J* = 9.0, 2.3 Hz, 1H); 6.73 (dd, *J* = 8.7, 4.2 Hz, 1H); 4.69-4.59 (m, 1H); 4.21-4.12 (m, 2H); 3.86-3.57 (m, 3H); 3.57-3.36 (m, 3H); 3.17 (s, 2H); 2.40-2.14 (m, 4H)
APCI-MS: *m/z* 527 (MH⁺)

20

Example 229

N-(5-Chloro-2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxyphenyl)urea trifluoroacetate (salt)

25 Step I:

5-Chloro-2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-[(4-methoxybenzyl)oxy]benzoyl azide

To a stirred slurry of 5-chloro-2-{{{(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-[(4-methoxybenzyl)oxy]benzoic acid

30 hydrochloride (235 mg, 0.4 mmol) in DCM (10 mL) triethylamine (60 μL, 0.4 mL) was

added to obtain a solution. To the solution diphenyl phosphoryl azide (90 μ L, 0.4 mmol) and triethylamine (60 μ L, 0.4 mmol) were added. The mixture was stirred at ambient temperature over night. The solvent was evaporated *in vacuo* and the residue purified by flash chromatography (silica, DCM) leaving the subtitled compound as an impure
5 colourless oil (235 mg), which was used in the next step without further purification.
APCI-MS: m/z 585 (MH^+ , isocyanate)

Step II:

***N*-(5-Chloro-2-{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)urea trifluoroacetate (salt)**
10

Crude 5-chloro-2-{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoyl azide (235 mg, < 0.4 mmol) was dissolved in toluene (3 mL) and heated while stirred for 3h. The yellow solution was cooled to ambient temperature and 0.5M ammonia in dioxane (1.6 mL, 0.8 mmol) was
15 added and the mixture was left over night. The solvent was evaporated *in vacuo* and the residue dissolved in 10% TFA in DCM (5 mL) and left for 1h. The solvent was evaporated *in vacuo* and the dark residue purified by preparative HPLC using acetonitrile / water containing 0.1% TFA as mobile phase. The titled compound was obtained as a white amorphous solid after freeze drying (6 mg, 2.5 %).

20 1H -NMR (Aceton- d_6 , 400 MHz): δ 8.35 (s, 1H), 7.70 (br. s, 1H), 7.25 (s, 1H), 7.14 (dd, J = 8.5, 2.0 Hz, 1H), 6.77 (d, J = 8.5 Hz, 1H), 6.65 (s, 1H), 5.92 (br. s, 2H), 4.54 (m, 1H), 4.14 (d, J = 9.7 Hz, 1H), 4.02 (dd, J = 9.4, 5.1 Hz, 1H), 3.95 - 3.65 (m, 2H), 3.60 - 3.39 (m, 4H), 3.21 (s, 2H), 2.43 - 2.18 (m, 4H)

APCI-MS: m/z 482 (MH^+)

Example 230

***N*-(5-Chloro-2-{[(2*S*)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)urea trifluoroacetate (salt)**

The compound was prepared from 5-chloro-2- $\{[(2S)$ -3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ -4-[(4methoxybenzyl)oxy]-benzoic acid as described in Example 229.

APCI-MS: m/z 466 (MH^+)

5

Example 231

N-(5-chloro-2- $\{[(2S)$ -3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy $\}$ phenyl)urea

10 Step I:

N-(5-chloro-2-hydroxyphenyl)urea

2-amino-4-chlorophenol (1.3 g, 8.9 mmol) was dissolved in 1M HCl (10 mL). Ammonium acetate was added to the solution to adjust pH to 5. The stirred mixture was treated with a suspension of potassium cyanate (0.80 mg, 9.8 mmol) in water, and then kept overnight at room temperature. Water was removed by evaporation and the residue was recrystallized from water to afford pink precipitate (0.9 g, 55 %).

15

APCI-MS: m/z 187 [MH^+]

Step II:

20 *N*-{5-chloro-2-[(2*S*)-oxiran-2-ylmethoxy]phenyl}urea

A solution of *N*-(5-chloro-2-hydroxyphenyl)urea (0.9 g, 4.9 mmol) and (2*S*)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (1.0 g, 3.8 mmol) in dimethylformamide were stirred under nitrogen. Cesium carbonate (1.9 g, 5.7 mmol) was added to the mixture and the reaction was stirred under nitrogen at room temperature over night. The mixture was partitioned between water and dichloromethane, and the organic phase was washed with water. After drying, filtration and evaporation of the solvent 0.48g, (52 %) of subtitle compound was obtained.

25

APCI-MS: m/z 243 [MH^+].

30 Step III:

***N*-(5-chloro-2-{[(2*S*)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)urea**

N-(5-chloro-2-[(2*S*)-oxiran-2-ylmethoxy]phenyl)urea (0.48 g, 2.0 mmol) and 5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (0.49 g, 2.0 mmol) were dissolved in 3 mL ethanol.

5 The reaction mixture was stirred at 80°C over night. Ethanol was removed by evaporation and the mixture was purified by column chromatography (dichloromethane/methanol) and HPLC on C18 (Xterra) to afford 35 mg (39 %) of the title compound.

¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.18 (d, *J* = 2.6 Hz, 1H); 7.92 (s, 1H); 7.07-6.97 (m, 2H); 6.91-6.84 (m, 2H); 6.73-6.68 (m, 1H); 6.33 (s, 2H); 4.88 (br.s, 1H); 4.15-3.98 (m, 10 2H); 3.97-3.85 (m, 1H); 3.00 (s, 2H); 2.76-2.30 (br.m, 6H, partially covered with the signal of solvent); 1.94-1.65 (br.m, 4H).

APCI-MS: *m/z* 450 [MH⁺]

Example 232

15 ***N*-(5-chloro-2-{[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)urea**

The title compound was prepared using 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] as described in Example 231.

20 APCI-MS: *m/z* 466 [MH⁺]

Example 233

***N*-(2-{[(2*S*)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)urea**

25

The title compound was prepared from 2-aminophenol as according to the procedure described in Example 231.

¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.08-8.01 (m, 1H); 7.77 (s, 1H); 7.08-7.03 (m, 1H); 7.00-6.95 (m, 1H); 6.92-6.80 (m, 3H); 6.75-6.69 (m, 1H); 6.16 (s, 2H); 4.90 (br.s, 1H);

4.20-4.00 (br.m, 2H); 3.97-3.86 (m, 1H); 3.02 (s, 2H); 2.86-2.35 (br.m, 6H, partially covered with the signal of solvent); 2.02-1.67 (br.m, 4H).

APCI-MS: m/z 416.2 [MH⁺]

5 **Example 234**

N-(2-([(2*S*)-2-hydroxy-3-(1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}phenyl)urea

The title compound was prepared from 2-aminophenol and 3*H*-spiro[1-benzofuran-2,4'-piperidine] according to the procedure described in Example 231.

¹H-NMR (acetone-*d*₆, 400 MHz): δ 8.25-8.21 (m, 1H); 7.81 (br.s, 1H); 7.17-7.13 (m, 1H); 7.10-7.04 (m, 1H); 7.02-6.96 (m, 1H); 6.92-6.84 (m, 2H); 6.81-6.75 (m, 1H); 6.69 (d, *J* = 7.6 Hz, 1H); 5.60 (br.s, 2H); 4.18-4.09 (m, 2H); 4.02-3.94 (m, 1H); 3.01 (s, 2H); 2.82-2.53 (m, 6H, partially covered with the signal of solvent); 1.95-1.77 (m, 4H).

15 APCI-MS: m/z 398 [MH⁺]

Example 235

N-(4-fluoro-2-([(2*S*)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)urea

20

The title compound was prepared from 2-amino-5-fluorophenol and 5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine] according to the procedure described in Example 231.

¹H-NMR (acetone-*d*₆, 400 MHz): δ 8.17 (dd, *J* = 9.0, 6.4 Hz, 1H); 7.75 (br.s, 1H); 6.97-6.92 (m, 1H); 6.87-6.79 (m, 2H); 6.69-6.60 (m, 2H); 5.68 (br.s, 2H); 4.21-4.12 (m, 2H); 4.06-3.97 (m, 1H); 3.04 (s, 2H); 2.81-2.55 (m, 6H, partially covered with the signal of solvent); 1.97-1.79 (m, 4H).

25

APCI-MS: m/z 434.2 [MH⁺]

Example 236

***N*-(4-fluoro-2-{{[(2*S*)-2-hydroxy-3-(1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}phenyl)urea**

- 5 The title compound was prepared from 2-amino-5-fluorophenol and 3*H*-spiro[1-benzofuran-2,4'-piperidine] according to the procedure described in Example 231.
- ¹H-NMR (acetone-*d*₆, 400 MHz): δ 8.21-8.15 (m, 1H); 7.71 (br.s, 1H); 7.15 (d, *J* = 7.3 Hz, 1H); 7.07 (t, *J* = 7.7 Hz, 1H); 6.88-6.82 (m, 1H); 6.79 (t, *J* = 7.4 Hz, 1H); 6.69 (d, *J* = 7.9 Hz, 1H); 6.67-6.60 (m, 1H); 5.64 (br.s, 2H); 4.22-4.11 (m, 3H); 4.05-4.00 (m, 1H); 3.02 (s, 10 2H); 2.90-2.57 (m, 6H, partially covered with the signal of solvent); 1.97-1.79 (m, 4H).
- APCI-MS: *m/z* 416.2 [MH⁺]

THP-1 Chemotaxis Assay**15 Introduction**

The assay measured the chemotactic response elicited by MIP-1α chemokine in the human monocytic cell line THP-1. The compounds of the Examples were evaluated by their ability to depress the chemotactic response to a standard concentration of MIP-1α chemokine.

20

Methods**Culture of THP-1 cells**

- Cells were thawed rapidly at 37°C from frozen aliquots and resuspended in a 25 cm flask containing 5 ml of RPMI-1640 medium supplemented with Glutamax and 10% heat 25 inactivated fetal calf serum without antibiotics (RPMI+10%HFCS). At day 3 the medium is discarded and replaced with fresh medium.

THP-1 cells are routinely cultured in RPMI-1640 medium supplemented with 10% heat inactivated fetal calf serum and glutamax but without antibiotics. Optimal growth of the

cells requires that they are passaged every 3 days and that the minimum subculture density is 4×10^5 cells/ml.

Chemotaxis assay

- 5 Cells were removed from the flask and washed by centrifugation in RPMI+10%HIFCS+glutamax. The cells were then resuspended at 2×10^7 cells/ml in fresh medium (RPMI+10%HIFCS+glutamax) to which was added calcein-AM (5 μ l of stock solution to 1 ml to give a final concentration of 5×10^{-6} M). After gentle mixing the cells were incubated at 37°C in a CO₂ incubator for 30 minutes. The cells were then diluted to
- 10 50 ml with medium and washed twice by centrifugation at 400xg. Labelled cells were then resuspended at a cell concentration of 1×10^7 cells/ml and incubated with an equal volume of MIP-1 α antagonist (10^{-10} M to 10^{-6} M final concentration) for 30 minutes at 37°C in a humidified CO₂ incubator.
- 15 Chemotaxis was performed using Neuroprobe 96-well chemotaxis plates employing 8 μ m filters (cat no. 101-8). Thirty microlitres of chemoattractant supplemented with various concentrations of antagonists or vehicle were added to the lower wells of the plate in triplicate. The filter was then carefully positioned on top and then 25 μ l of cells preincubated with the corresponding concentration of antagonist or vehicle were added to
- 20 the surface of the filter. The plate was then incubated for 2 hours at 37°C in a humidified CO₂ incubator. The cells remaining on the surface were then removed by adsorption and the whole plate was centrifuged at 2000 rpm for 10 minutes. The filter was then removed and the cells that had migrated to the lower wells were quantified by the fluorescence of cell associated calcein-AM. Cell migration was then expressed in fluorescence units after
- 25 subtraction of the reagent blank and values were standardized to % migration by comparing the fluorescence values with that of a known number of labelled cells. The effect of antagonists was calculated as % inhibition when the number of migrated cells were compared with vehicle.